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TREATMENT OF MULTIPLE SCLEROSIS WITH NICOTINIC ACID AND VITAMIN B₁

PRELIMINARY REPORT

MATTHEW T MOORE, M D

PHILADELPHIA

The treatment of advanced multiple sclerosis with nicotinic acid and a combination of nicotinic acid and thiamin chloride has yielded promising results in cases in which the patients have failed to respond to therapies hitherto used. While complete remission has not been obtained, the use of the treatment suggested here has resulted in continued symptomatic improvement. The potential value of the suggested treatment may be judged in the light of prevailing conceptions of the etiology and treatment of multiple sclerosis.

From 1838, when Sir Robert Carswell, as cited by Putnam,¹ first described the pathology of multiple sclerosis, up to the present, the treatment of this disease has been entirely empiric. When one examines the diversity of remedial agents and methods employed, it becomes evident that the disarray is occasioned by complete ignorance of the etiology of the disease, coupled with the desire to find a remedy for one of the most perplexing and frequently occurring nervous ailments.²

Many hypotheses have been advanced regarding the etiology of multiple sclerosis, endotoxins and exotoxins,³ specific organisms,⁴ virus

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From the Jewish Hospital and the John L. Eckel Neuropathological Laboratory, University of Pennsylvania Graduate School of Medicine

1 Putnam, T. J. The Centenary of Multiple Sclerosis, *Arch Neurol & Psychiat* **40** 806 (Oct) 1938

2 Bram, W. R. Critical Review Disseminated Sclerosis, *Quart J Med* **23** 343 (April) 1930. Problems of Disseminated Sclerosis, editorial, *J Neurol & Psychopath* **13** 227 (Jan) 1933

3 (a) Hassin, G. The Pathogenesis of Multiple Sclerosis, *Arch Neurol & Psychiat* **7** 589 (May) 1922. (b) Brickner, R. M. Studies on the Pathogenesis of Multiple Sclerosis, *ibid* **23** 715 (April) 1930. (c) Jelliffe, S. E., and White, W. A. Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1923, p. 562. (d) Steiner, G. Multiple Sclerosis: The Etiological Significance of the Regional and Occupational Incidence, *J Nerv & Ment Dis* **88** 42 (July) 1938

(Footnote continued on next page)

infection,⁵ trauma,^{3c} vascular disturbances⁶ and vitamin deficiency⁷ are some of the many factors which have been charged with producing the disease. The variety and uncertainty of the etiologic theories advanced are reflected in the forms of treatment which have been used. Gowers,⁸ in 1888, suggested the use of arsenic, silver nitrate and quinine, Oppenheim,⁹ in 1908, recommended Credé's silver ointment,¹⁰ application of the galvanic current to the back or head, local blood letting (by leeches) and Nauheim baths. Brickner,¹¹ in an excellent summary of the therapy of multiple sclerosis, listed an imposing array of remedies, including, among others, various preparations of antimony and arsenic, fever induced by various methods (diathermy, malaria, typhoid vaccine), fever in conjunction with drugs, surgical procedures (cervical sympathectomy, root section, etc.), germanin (reported to be a sodium salt of symbis [*m*-aminobenzoyl-*m*-amino-*p*-methylbenzoyl-*l*-naphthylamino-4,6,8-trisulfonic acid] urea), serums, hypnotism, intraspinal injection of lecithin, vaccines and quinine hydrochloride.

Recently, emphasis has been laid etiologically on the possible implications⁶ of vascular lesions and therapeutically on the employment of fever therapy to promote hyperemia and an increased flow of blood in nerve tissue. The application of fever therapy in its various forms (malaria, typhoid vaccine, hot baths, diathermy, the Kettering hypertherm) has many annoying disadvantages, and indeed dangers,¹² which should make welcome a less disturbing method of inducing the changes wrought by

4 Bullock, W. E. The Experimental Transmission of Disseminated Sclerosis, *Lancet* **2** 1185, 1913. Steiner, G. Multiple Sklerose, *Therap. Halbmonatsh.* **34** 68 (Feb. 1) 1920. Schuster, G. Spirochetes in the Etiology of Certain Paralyzes, *Lancet* **1** 21 (Jan. 1) 1921.

5 Chevassut, K. Aetiology of Disseminated Sclerosis, *Lancet* **1** 552 (March 15) 1930. Purves-Stewart, J. A Specific Vaccine Treatment in Disseminated Sclerosis, *ibid.* **1** 560 (March 15) 1930.

6 Putnam, T. J. The Pathogenesis of Multiple Sclerosis. A Possible Vascular Factor, *New England J. Med.* **209** 876 (Oct. 19) 1933. Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," *Arch. Neurol. & Psychiat.* **37** 1298 (June) 1937.

7 Zimmerman, H. M., and Burack, E. Lesions of the Nervous System Resulting from a Deficiency of the Vitamin B Complex, *Arch. Path.* **13** 207 (Feb.) 1932.

8 Gowers, W. R. A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston, Son & Co., 1888, p. 930.

9 Oppenheim, H. Text-Book of Nervous Diseases, translated by A. Bruce, ed. 5, Edinburgh, Otto Schulze & Co., 1911, vol. 1, pp. 33 and 350.

10 Credé's ointment contains 15 per cent of collargol (a proprietary preparation of colloidal silver and silver nitrate, stabilized by egg albumin), 5 per cent of water, 10 per cent of white wax and 70 per cent of benzoinated lard.

11 Brickner, R. M. A Critique of Therapy in Multiple Sclerosis, *Bull. Neurol. Inst. New York* **4** 665 (April) 1936.

this treatment Smith, Ruffin and Smith¹³ reported the successful treatment of pellagra with nicotinic acid and described the reaction following the intramuscular administration of 60 mg of nicotinic acid, "a marked flushing of the face, neck, chest and arms appeared a few minutes after intramuscular injection and lasted fifteen minutes" Similar flushing occurred after the intravenous use of the drug which had been dissolved in a solution of 5 per cent dextrose in physiologic solution of sodium chloride No discomfort was experienced by the patient

The description of marked flushing of the skin led me to consider the feasibility and advisability of using nicotinic acid in cases of multiple sclerosis and to attempt to determine whether the cerebrospinal nervous system becomes hyperemic in a manner similar to that observed in the skin If the answer to this query were in the affirmative, some of the beneficial effects of fever therapy might be realized by the use of this substance and the baneful side effects eliminated

MATERIAL AND METHOD

The 5 cases reported here represent, in the main, advanced multiple sclerosis Nicotinic acid therapy was begun in the first case on Feb 15, 1938, and has been used almost continuously, with a few interruptions, until the time of writing Until June 1938 the nicotinic acid was given intramuscularly and intravenously on alternate week days The intramuscular dose varied from 60 to 120 mg, dissolved in 10 cc of sterile physiologic solution of sodium chloride The intravenous dose varied from 60 to 160 mg, dissolved in 1,000 cc of 5 per cent dextrose in sterile physiologic solution of sodium chloride, and was given over a period of approximately one hour After June 4, 1938 the drug was given intramuscularly exclusively, in doses varying from 80 to 140 mg, two or three times weekly, depending on the patient's reaction At this time the use of vitamin B₁ (thiamin chloride) was begun, and it was administered intravenously in doses of 3.32 mg (10,000 international units) at the height of the cutaneous hyperemia After July 18 the nicotinic acid and thiamin chloride were given combined in solution with sterile distilled water, each cubic centimeter representing 12 mg of nicotinic acid and 3.32 mg of thiamin chloride Ten cubic centimeters of this solution was the average intramuscular dose, given into the buttocks It was found that unless the solution was heated to about 110 F and drawn into a warm syringe barrel immediately before injection the characteristic flushing of the skin and pervading body warmth did not develop with any degree of intensity

In 2 cases thermocouple records of skin temperatures were made to determine the degree of hyperemia, and in addition (on another occasion) studies of the

12 (a) Bennett, A E Evaluation of Artificial Fever Therapy for Neuropsychiatric Disorders, *Arch Neurol & Psychiat* **40** 1141 (Dec) 1938 (b) Collins, R T Transitory Neurological Changes During Hyperthermia, *Bull Neurol Inst New York* **7** 291 (Dec) 1938

13 Smith, D T, Ruffin, J M, and Smith, S G Pellagra Successfully Treated with Nicotinic Acid A Case Report, *J A M A* **109** 2054 (Dec 18) 1937

cerebrospinal fluid pressure (expressed in millimeters of cerebrospinal fluid) were made before and during the appearance of the skin reaction. Oral temperatures were also taken at this time. Electrocardiographic studies were performed on 3 patients before the use of nicotinic acid was begun and several months thereafter, to ascertain any changes attributable to its use.

As a result of the finding of increased cerebrospinal fluid pressures and in an attempt to answer the query originally posed regarding the possible hyperemia of the central nervous system following the use of nicotinic acid, preparations of the cat's brain and cervicothoracic portion of the cord were made to demonstrate the reaction of the pial vessels to intramuscular use of the drug. With the animal under anesthesia induced with sodium amytal (50 mg per kilogram of body weight given intraperitoneally), the brain and spinal cord (lower cervical and upper thoracic portions) were exposed and the pial vessels photographed before and five and ten minutes after the intramuscular injection of 4 cc (48 mg) of a solution of nicotinic acid. The photographic technic with regard to intensity of light, distance and other factors was constant throughout. The photographs were enlarged 24 diameters to show any changes in the size of the arterial vessels and any increase in the number of vessels perceptible.

REPORT OF CASES

CASE 1—E. N., a white man aged 38, married, gave the history of an onset of uncertain gait and ready fatigability in June 1933. Because of incoordination and easy fatigue he was compelled to quit his work in the delivery room of a newspaper. When first examined by me in June 1934, he showed bilateral temporal pallor of the optic disks, nystagmus on horizontal and vertical gaze, thick spastic speech, exaggerated tendon reflexes in the upper and lower limbs, loss of abdominal reflexes, diminished cremasteric reflexes, bilateral Hoffmann, Babinski, Chaddock and Oppenheim signs, loss of vibration sense in the malleoli of both feet, impairment of the senses of position and passive motion in the lower limbs, and a spastic, dancing gait. Examination of the cerebrospinal fluid showed 5 cells per cubic millimeter, a negative Wassermann reaction, a colloidal gold curve characteristic of dementia paralytica and 20 mg of protein. Hematologic studies and the Wassermann test of the blood gave normal results. Other laboratory studies revealed nothing abnormal. The patient was placed on a high vitamin diet and given quinine bisulfate, 5 grains (0.325 Gm), two or four times a day, for over two months, without showing appreciable change. During August 1934 he began the first series of ten weekly treatments with the Kettering hypertherm. The usual procedure for inducing hyperpyrexia was followed in this and in subsequent treatments. Slight subjective improvement lasted about one month, followed by a decline. A second series of eleven treatments with the Kettering hypertherm was given in 1935, after which there was improvement in speech. Two more series of inductions of hyperpyrexia were given, beginning May 1936 and January 1937, respectively, the total number of treatments being thirty-nine. His condition became progressively worse, and he was compelled to use an improvised walker to get about. In addition to intensification of the findings at the first examination, there were a positive Romberg sign, bilateral ankle clonus, intention tremor and marked difficulty in arising from the seated position and in sitting down. Five cubic centimeters of histidine monohydrochloride (larostidin) was given daily intramuscularly from April 27 to May 7, 1937, without change.

On Feb 15, 1938, he was given for the first time 60 mg of nicotinic acid dissolved in 10 cc of sterile physiologic solution of sodium chloride, injected into the buttock. In three minutes there was a subjective feeling of warmth in the face and neck, and in five minutes flushing of the face, neck and shoulders appeared, extending later to the chest and back. This flushed appearance lasted forty-five minutes. There was no appreciable change in pulse or blood pressure. Oral temperatures taken at the time of flushing showed no rise above normal. The patient was given intramuscular and intravenous injections alternately on week days until June 4, 1938. The intravenous injections consisted of 120 mg of nicotinic acid dissolved in 1,000 cc of 5 per cent dextrose in physiologic solution of sodium chloride, which was given over a period of one hour. With intravenous administration the flushing did not appear as rapidly or as intensely as with intramuscular injection. By June there was considerable subjective and

TABLE 1—*Thermocouple Readings of Skin Temperature (Case 1) Following Intravenous Injection of 1,000 Cc of 5 per Cent Dextrose in Physiologic Solution of Sodium Chloride Containing 140 Mg of Nicotinic Acid*

Skin Temperature, Degrees, C	Forehead	Lobe Left Ear	Lobe Right Ear	Left Zygoma	Right Zygoma	Anterior Portion of Neck	Left Shoulder	Right Shoulder	Dorsum of Third Finger	Chest, Left Side	Chest, Right Side
Before injection	32.0	32.0	31.0	34.0	34.3	34.1	33.4	33.1	33.5	32.8	32.8
10 min after injection	33.0	34.0	34.0	35.0	35.2	35.0	34.3	33.8	33.8	33.4	33.6
12 min after injection	35.2	35.2	35.2	35.8	35.8	35.8	34.0	34.3	34.0	34.2	34.2
14 min after injection	35.3	35.5	35.5	35.8	35.8	35.6	34.5	34.6	34.0	34.3	34.3
Maximum rise	3.3	3.5	4.5	1.8	1.5	1.7	1.1	1.5	0.5	1.5	1.5

objective improvement. Subjectively, the patient noted greater ease of movements and less stiffness of his limbs, there was also improvement in the gnostic sense. He was able to walk without the aid of the walker and arose from the sitting position with less difficulty than previously. Coordination had improved, as shown by the various tests. On June 4 vitamin B₁ (thiamin chloride) therapy was begun. Injections of 10,000 international units of crystalline vitamin B₁ (33.2 mg of thiamin chloride) dissolved in 1 cc of sterile distilled water were given intravenously at the height of the skin flushing. This was done three times a week until July 18, 1938, when the thiamin chloride (33.2 mg) was combined with nicotinic acid (120 mg) in 10 cc of sterile distilled water and given intramuscularly. On September 8 therapy was discontinued for three weeks to see if any change occurred. The patient began to show return of the marked spasticity and was compelled to resort to use of the walker. He complained of difficulty in moving his body and in sitting and arising. When the nicotinic acid and vitamin B₁ therapy was renewed he noted improvement within several days. Complete remission was not obtained, but he felt distinctly better able to walk and maneuver his body than previous to this form of medication. Laboratory studies

of the urine and blood gave essentially normal results. Roentgen studies showed that the skull and vertebral column were entirely normal. Repeated Queckenstedt tests revealed no evidence of cerebrospinal fluid block. Electrocardiographic studies made prior to the use of nicotinic acid and again on October 21 showed no appreciable difference in the tracings. Thermocouple readings of skin temperature taken on May 25, 1938, when an intravenous injection of 1,000 cc of 5 per cent dextrose in physiologic solution of sodium chloride containing 140 mg of nicotinic acid was given, are shown in table 1. On October 15 a lumbar puncture was performed, with the patient in the recumbent position, and pressure readings,

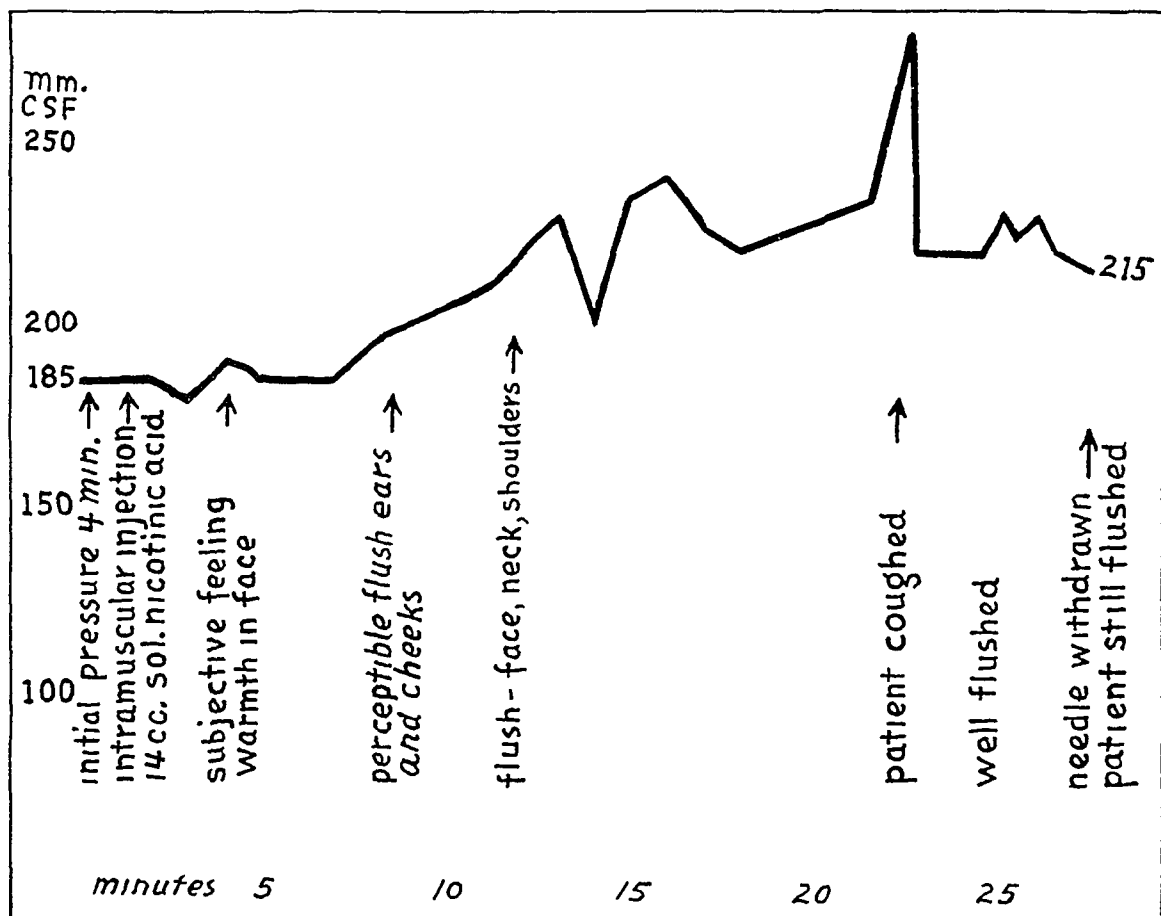


Fig 1 (case 1) —Manometric readings showing a sustained rise of cerebrospinal fluid pressure coincident with the active flushing of the skin following intramuscular injection of a solution of 168 mg of nicotinic acid

expressed in millimeters, of cerebrospinal fluid, were made at thirty second intervals for twenty-five minutes, the pressures were noted previous to and after the intramuscular injection of 14 cc of a solution containing 12 mg of nicotinic acid per cubic centimeter of distilled water

CASE 2—E I, a white woman aged 47, a housewife, first noticed difficulty in walking during the summer of 1934. At first her left leg gave way under her, and then both legs became involved. She tired easily when walking and experienced an occasional "peculiar numbness" of her lower limbs. At times she felt an electric-like sensation along her spine. She also complained of urgency in

urination. She received manipulative treatments, but despite this her condition became worse. When I first examined her in October 1935, she complained of the symptoms mentioned, plus difficulty in playing the piano because of slight stiffness of her fingers. Examination showed temporal pallor of both optic disks, incoordination in the finger to nose test, exaggerated biceps and triceps reflexes, more marked on the left, a Hoffmann sign bilaterally, that on the left side predominating, absence of abdominal reflexes, exaggerated knee jerks and a more marked ankle jerk on the left, a Babinski sign and ankle clonus bilaterally, and a spastic ataxic gait. Laboratory studies performed in December 1935 showed that the blood and urine were normal, the Queckenstedt test revealed no evidence of cerebrospinal fluid block, examination of the cerebrospinal fluid showed 10 cells per cubic millimeter, a negative Wassermann reaction, a colloidal gold curve of 1123220000 and a negative Wasseimann reaction of the blood. Roentgenographic studies of the skull and vertebral column showed nothing abnormal. The patient was given a series of hyperpyrexia treatments, typhoid vaccine being given intravenously, in addition, forced cerebrospinal fluid drainage was carried out by the method of Retan. There was a moderate degree of improvement for several months in the subjective feeling of less stiffness of the limbs and in walking. Later there was a gradual decline, however, and quinine bisulfate was given in doses of 10 to 20 grains (0.65 to 1.3 Gm.) daily, depending on the degree of tolerance. No appreciable subjective or objective change was noticed, in fact during July 1936 complete paraplegia developed, lasting three weeks, from which the patient slowly recovered. Several alternating courses of bismuth, mercury and iodides produced no change. Again during the summer of 1937 marked difficulty in standing developed, the patient being unable to walk, and she was entirely unable to play the piano. There were extreme incoordination and ataxia. A second series of hyperpyrexia treatments with typhoid vaccine failed to alter the downhill course.

On March 3, 1938, treatment with nicotinic acid was begun, and the method of injection outlined under "Material and Method" was carried out. A description by the patient of the sensations she experienced after an injection of nicotinic acid and vitamin B₁ follows:

"Within a few seconds to half a minute there is a sulfur-like taste in the mouth. Three minutes after injection a flush begins in the face, accompanied by a hot prickly sensation, it spreads quickly to the chest, thence it begins creeping down the arms to the elbows, then on down to the finger tips—the third finger in each hand feeling it especially, a tingling with tight sensation at the tip. It continues creeping down the body to the hips. In fifteen minutes the tingling sensation reaches the knees and begins to recede from the face and to increase in the lower limbs, the knees are hot, but the ankles are cold. The tingling sensation begins in the feet, though the feet are still cold. Marked stiffness in the legs begins. In twenty-five minutes the legs below the knees begin to feel hot. In thirty minutes the feet begin to get hot and prickly. The face is still flushed, but tingling is only slight. In forty-five minutes the sensation of heat is still increasing. In one hour the legs are extremely stiff and hot. There is slight headache. The flush has gone from the face and chest. There is loss of appetite. At two hours, after arising, there is an odd sensation along the spinal column, such as when the back is very tired. Otherwise the condition is unchanged. The sensation of heat is still increasing in the feet after two and a half hours. After five or six hours the lower limbs are just comfortably warm. By the following afternoon the stiffness in the lower limbs begins to wear off. After injection there is noticeable absence of pains in the legs and ankles, there is a stretchy, pully feeling during the night, a sensation of 'going to sleep' comes on after sitting still for a while."

Within two weeks after treatment was instituted she noticed improvement in walking and began to regain her ability to play the piano. The sensation of numbness of her lower limbs disappeared within six to eight weeks. On two occasions therapy was stopped for two weeks in order to determine if any change would occur. During one of these interludes injections of sterile distilled water were substituted. During each two week interval there were a definite increase in spasticity of the four limbs, great difficulty in walking and increased incoordination and ataxia of the upper limbs. She insisted that a change for the worse had taken place. On returning to the use of nicotinic acid and thiamin chloride she noticed appreciable lessening of spasticity, and at the time of writing she can play the piano fairly well and walk about the house, albeit in a spastic manner. The exaggerated tendon reflex activity, pathologic reflexes and sensory changes have not altered. Disturbances of the bowel or bladder have not supervened.

CASE 3—A L, a white woman aged 49, in 1928 noticed unsteadiness of gait, which was followed in a short time by inability to walk without assistance. Speech difficulty developed. Examination showed a labored, spastic gait and dragging of both feet when using an improvised supportive walker (she was unable to walk without its aid), incoordination and ataxia of the upper limbs, exaggerated tendon reflexes throughout, absence of abdominal reflexes, a Babinski sign bilaterally and marked pallor of the temporal aspects of both disks. She had great difficulty in moving her body and in getting out of bed. In February 1937 she was given quinine bisulfate, 5 grains (0.325 Gm.), three times a day for approximately three months, without improvement. Later histidine monohydrochloride, 5 cc intramuscularly, was given daily for two months, and no improvement was noted. On March 1, 1938 nicotinic acid therapy was begun and carried out in a manner similar to that in the preceding cases. The cutaneous reaction to nicotinic acid was much the same as in case 1. There was no rise of oral temperature during the height of flushing of the skin. When thiamin chloride was added the patient noticed a peculiar taste in her mouth, but was unable to describe it. She began to notice improvement in walking about one month after therapy was begun. She stated that she no longer dragged her feet so much and was able to bend her legs at the knees and lift her feet from the ground. Later she noticed ease in moving her body and was elated about it. Changes in the objective neurologic signs were not noticed. This patient had invariably refused previous forms of treatment after a few months' trial when they failed to reward her with improvement, but she welcomed the injections of nicotinic acid and vitamin B₁ and requested their continuance.

Laboratory studies gave essentially normal results. Electrocardiographic studies, made on March 4 and Oct. 20, 1938, showed no change in the tracings on the two dates.

CASE 4—M P, a white man aged 32, formerly an electrician, dated his illness from 1927, when he complained of severe pains in the back of his neck. Shortly afterward staggering and uncertainty in walking appeared. The legs became stiff, and bladder disturbance appeared early in the course of the disease and has been present since. Speech difficulty began in 1930. He became increasingly spastic, and involvement of the arms recently developed. For the past one and a half years he has been unable to walk and uses a wheel chair.

In 1928 his condition was diagnosed as multiple sclerosis at a hospital for neurologic diseases, and germanin was administered from September 1928 to July 1929, without improvement. He was later treated at five other institutions, before entering the Jewish Hospital in April 1938. He had received quinine

bisulfate and hyperpyrexia treatments with diathermy and the Kettering hypertherm, and had been placed on a dehydration regimen, but at no time was a remission induced

In April 1938 he presented a picture of extreme boardlike spasticity of the lower limbs, which usually were crossed and which could not be uncrossed voluntarily. He had great difficulty in moving in bed and was unable to lift himself from the recumbent position. There were bilateral nystagmus, lateral and vertical, pallor of both disks, intention tremor, scanning speech, exaggerated biceps and triceps reflexes bilaterally, absence of cremasteric reflexes, spasticity of the legs so marked at times as to make it impossible to obtain the knee jerks, or to make them, when obtainable, greatly exaggerated, bilateral Babinski and Chaddock signs, and loss of sense of vibration and passive motion in the lower limbs. Hematologic studies, urinalysis, a Wassermann test of the blood and cerebrospinal fluid studies gave normal results. The Queckenstedt reaction was negative. Roentgenographic studies of the skull and vertebral column and pneumomyelographic

TABLE 2—*Thermocouple Readings of Skin Temperature (Case 4) Following Intramuscular Injection of 10 Cc of a Solution of Nicotinic Acid*

Skin Temperature, Degrees, C	Forehead	Lobe Right Ear	Lobe Left Ear	Right Malar Area	Left Malar Area	Anterior Portion of Neck	Right Shoulder	Left Shoulder	Right Side of Abdo- men	Left Side of Abdo- men	Dorsum, Right Hand	Dorsum, Left Hand	Right Knee	Left Knee
Before injection	35.4	32.2	33.4	35.4	35.6	36.2	35.4	35.4	35.4	35.4	34.2	34.8	34.4	33.4
12 min after injection	35.9	35.4	36.4	36.4	36.6	36.4	36.2	36.2	35.8	35.8	34.4	35.6	34.8	33.8
17 min after injection	37.4	35.4	36.4	37.6	37.8	37.4	36.6	36.4	36.2	36.4	35.6	36.4	35.4	34.6
22 min after injection	37.4	35.6	36.6	37.8	37.8	37.8	36.8	36.4	36.6	36.6	36.4	36.8	35.6	34.8
27 min after injection	38.2	36.6	37.4	38.4	37.6	37.4	36.8	36.2	36.4	36.6	36.8	36.8	35.6	35.2
32 min after injection	37.4	36.2	36.2	37.4	37.4	36.8	37.2	36.2	35.8	35.8	36.4	36.4	35.4	34.8
Maximum rise	2.8	.44	.40	.30	.22	.16	.18	.10	.12	.12	.26	.20	.12	.18

examination gave normal results. In the latter part of April 1938 vitamin B therapy was begun as outlined in the preceding cases. After injection of nicotinic acid there developed, beginning in about three minutes, redness of the face and neck and patchy flushing of the shoulders, arms and trunk and even the legs, the most intense of any of the reactions in patients receiving the drug. The first evidence of change was a subjective feeling of relaxation of the trunk and greater ease in moving his body. This occurred in June 1938, and in July he was able to uncross his legs voluntarily and to move them somewhat. His arms became less stiff, so that he could manipulate his wheel chair with increased facility. He managed to lift himself up in bed and to get in and out of bed, which previously was impossible. He invariably requested that the injections be continued after a brief interruption of treatment. The improvement has been limited thus far to a definite subjective feeling of lessening of rigidity and the objective finding of diminished spasticity of the lower limbs and trunk and improved coordination of the upper limbs. He is now able for the first time in years to stand while holding on to the bedstead. The pathologic neurologic signs are unchanged. Electrocardiograms taken on April 26 and Oct 20, 1938, showed no difference in the tracings as the result of treatment.

CASE 5—J D, a white man aged 29, a hardwood finisher by trade, noticed difficulty in walking in January 1935. The right leg was affected first, and he experienced numbness of the tips of the fingers of the left hand. In February 1935 he entered a hospital, where he received ten treatments with the Kettering

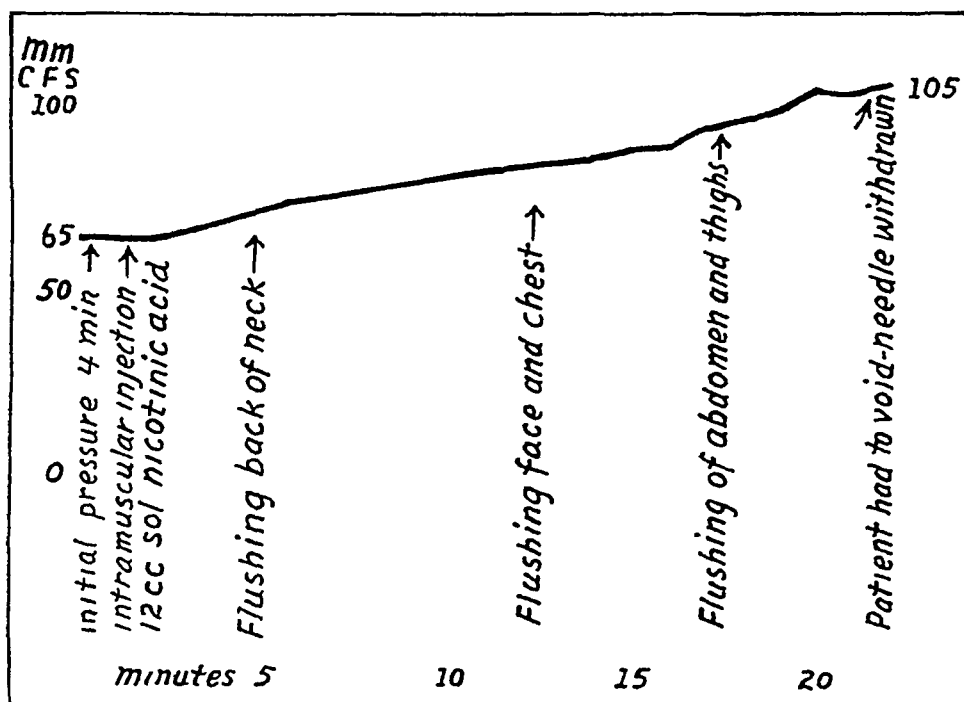


Fig 2 (case 4)—Manometric readings following the intramuscular injection of 10 cc of a solution of nicotinic acid (120 mg), showing the rise of cerebrospinal fluid pressure during the time of active flushing of the skin

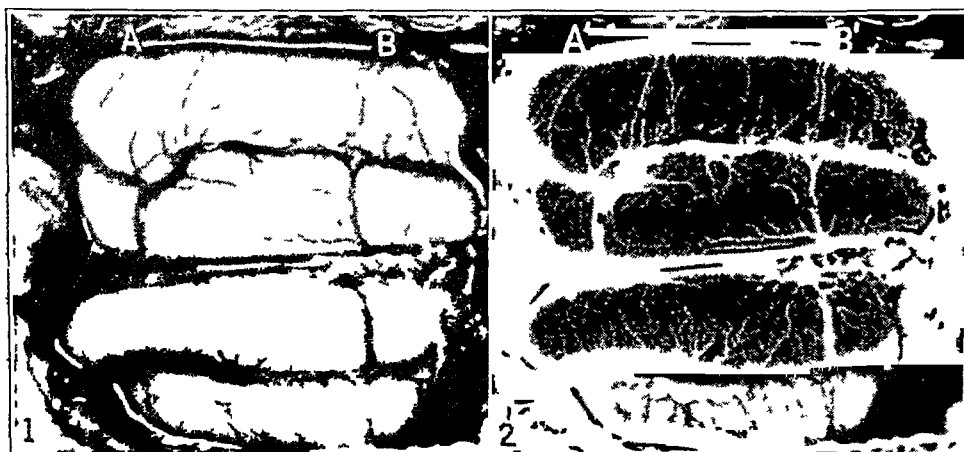


Fig 3—1, surface of a cat's brain before injection of nicotinic acid 2, five minutes after the intramuscular injection of 48 mg of nicotinic acid. Note the increased caliber of the large vessels and the duskiness of the cortex, due to the increased capillary filling

hypertherm. After leaving the hospital the left leg became stiff and weak, the right hand "curled up," and he had difficulty in straightening it. Both legs drew up and were very stiff. He had difficulty in starting the urinary stream and

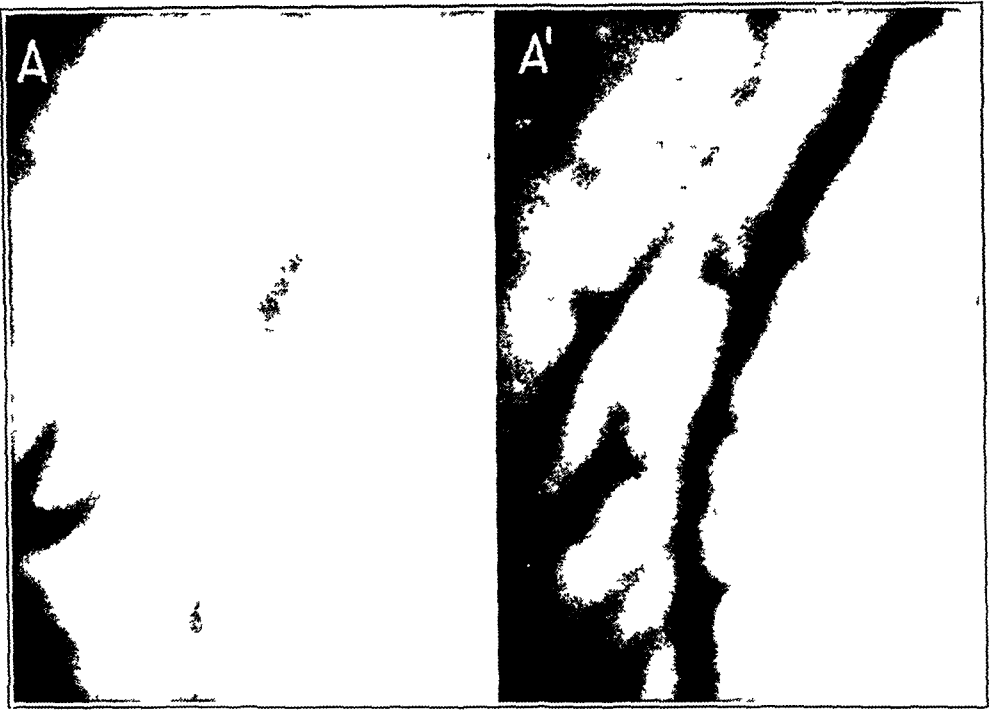


Fig 4—*A*, enlargement (24 diameters) of the pial artery shown in figure 3, 1*A* *A'*, the same vessel five minutes after intramuscular injection of 48 mg of nicotinic acid. There is not only an increase in the diameter of the arteries but an increased blood flow, as indicated by the photographic density of the arteries. Note also the increased number of smaller vessels visible.

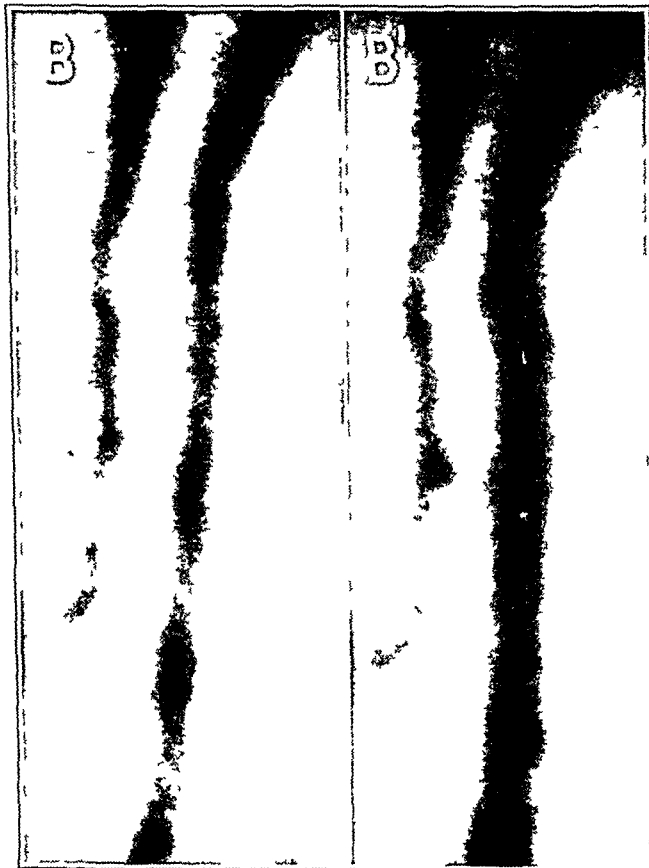


Fig 5—*B*, enlargement (24 diameters) of the pial artery shown in figure 3, 1*B* *B'*, the same vessel five minutes after injection of nicotinic acid.

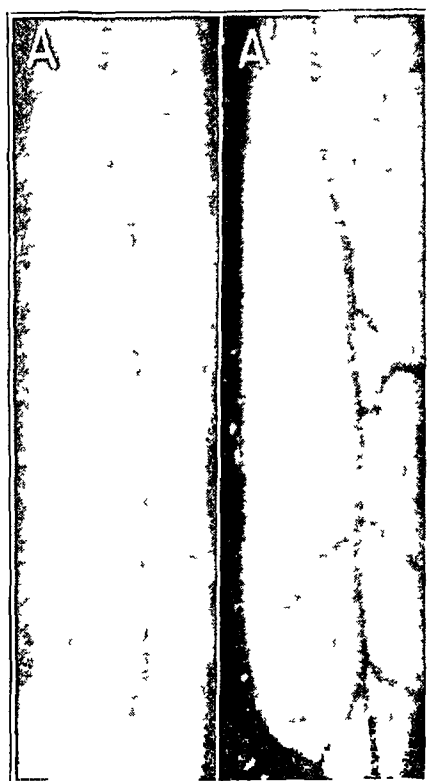


Fig 6—*A*, vessels on the dorsal aspect of the spinal cord previous to the injection of nicotinic acid *A'*, same vessels as those shown in *A* ten minutes after the intramuscular injection of 48 mg of nicotinic acid

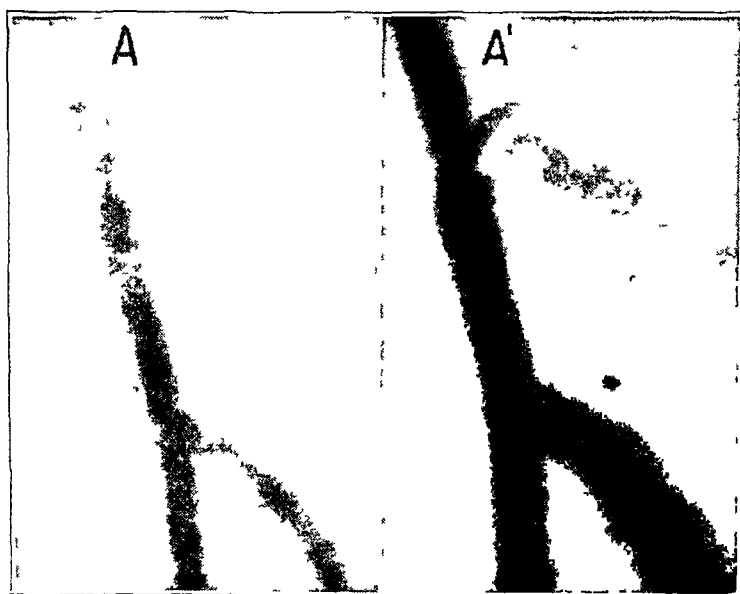


Fig 7—*A*, enlargement (24 diameters) of the vessel shown in figure 6 *A* *A'*, enlargement (24 diameters) of the same vessel ten minutes after the injection of nicotinic acid

trouble with his bowels. He entered another hospital, where he again was given ten hyperpyrexia treatments, without benefit. On May 24, 1938, he entered the Jewish Hospital. He then complained of marked stiffness of both legs, inability to walk or to move his body while in bed, weakness of both hands, numbness of both legs, "as if they were dead" and an electric-like sensation down his back, as well as the symptoms already enumerated. The significant neurologic findings were: temporal pallor of the right disk, atrophy of the intrinsic muscles of both hands, atrophy of the right forearm, marked weakness of both hands, with poor hand grip, incoordination of both upper limbs, exaggerated biceps and triceps reflexes, a Hoffmann sign bilaterally, absence of abdominal reflexes, exaggerated patellar and achilles reflexes bilaterally, bilateral Babinski and Chaddock signs, bilateral ankle clonus, spontaneous clonus of both legs whenever he attempted to lift himself in bed, loss of the senses of vibration and position in the lower limbs, foot drop, and inability to move his toes. He was unable to use his arms in feeding or dressing himself and could not hold a cigaret when he desired to smoke. Hematologic studies, urinalysis, serologic tests and examination of the spinal fluid gave normal results. The Queckenstedt reaction was negative. Roentgen studies of the skull and entire vertebral column showed no abnormalities.

Treatment with nicotinic acid was begun May 31, 1938, and the combined nicotinic acid-vitamin B₁ therapy was started on June 9. Within one week he noticed increased strength in his hand grip, and he had begun to move his toes. By July 9 he was able to move his body freely and was able to sit up in bed and in an armchair. The marked rigidity of the legs had diminished greatly. He stopped treatment for two months, and during this time there was considerable regression, but not to his previous state. Treatment was resumed Sept. 10, 1938, with three injections weekly. He noticed improvement in a short time, with decrease in spasticity and cessation of the electric-like sensation in his spine, and for the first time he was able to use his hands in eating, smoking and dressing. He stated that with this form of treatment he had greater use of his limbs and body than at any time since he completed his first series of hyperpyrexia treatments, in the spring of 1935. This patient noted also the sulfur-like taste within eight to fifteen seconds after injection of the mixed drugs.

COMMENT

The disease in the cases described may be classified as belonging to the intermediate and helpless stages, and as being of the chronic progressive type without remissions.¹¹ Prior to the use of nicotinic acid and vitamin B₁, the patients received in the aggregate the following forms of treatment: quinine bisulfate, germanin, high vitamin diet, hyperpyrexia (typhoid vaccine intravenously, diathermy, Kettering hypertherm), forced cerebrospinal fluid drainage, and histidine monohydrochloride.

Of the various therapies employed, hyperpyrexia appeared to produce a temporary improvement in most instances, except in case 5, in which the patient was made worse. In no instance did hyperpyrexia consummate a remission. In fact, after the short-lived improvement the patients stated that there was a noticeable decline in their ability to get about. It is evident that certain biochemical and physiologic changes occur incident to fever therapy, irrespective of the method of induction, which

bring about improvement during the course of the treatment and for a short time thereafter Bennett ^{12a} stated

The common denominator of all methods, whether employing infectious, biologic, chemical or physical means, is simply increased body temperature or artificial fever. Fever per se increases the velocity of the blood, produces vasodilatation and elevates the basal metabolism.

Regarding the use of fever in treatment of multiple sclerosis, Bennett ^{12a} said

Artificial fever therapy produces no permanent therapeutic effects which alter the course of the disease. In certain early stages of the disease it may produce transient temporary remissions, but in advanced stages it is of little or no value and may do harm.

This conclusion was not shared by such investigators as Stephenson,¹⁴ Dreyfus and Mayer,¹⁵ Schmidt and Weiss,¹⁶ Neymann and Osborne¹⁷ and Weiss,¹⁸ who presented a more optimistic picture of the results obtained by hyperpyrexia. The factors of vasodilatation and increased blood flow, as observed in fever therapy, result in an increase in tissue oxidation and nutrition.

Vasodilatation and increased blood velocity affecting the brain and spinal cord may be induced by ganglionectomy and sympathectomy. Favorable results have been reported by Wetherell,¹⁹ Royle²⁰ and Koch and de Savitsch.²¹ In fever therapy the process of vasodilatation and increased blood velocity is essentially a generalized one, whereas after ganglionectomy or sympathectomy the resultant vasodilatation lies within the area supplied by the removed stellate or sympathetic ganglia. The beneficial effects of vasodilatation and increased blood flow achieved by fever therapy and sympathectomy can be obtained through the use

14 Stephenson, J. Diathermy in Multiple Sclerosis. Report of Progress, *Physical Therap* **46** 373 (Aug.) 1928.

15 Dreyfus, G. L., and Mayer, K. Vier Jahre Malariaabehandlung der multiplen Sklerose, *Deutsche Ztschr. f. Nervenheilk.* **111** 68, 1929.

16 Schmidt, W. H., and Weiss, B. P. Fever Produced by Diathermy. Its Value in Multiple Sclerosis and Other Chronic Diseases, *Physical Therap* **49** 336 (Sept.) 1931.

17 Neymann, C. A., and Osborne, S. L. The Treatment of Some Multiple Sclerotics by Electropyrexia, *J. Nerv. & Ment. Dis.* **79** 423 (April) 1934.

18 Weiss, B. P. Further Observations on the Treatment of Multiple Sclerosis by Hyperpyrexia, *M. Rec.* **142** 489 (Dec. 4) 1935.

19 Wetherell, F. Multiple Sclerosis. Cervicodorsal Sympathectomy as a Relief Measure, Report of a Case, *J. A. M. A.* **102** 1754 (May 26) 1934.

20 Royle, N. D. The Surgical Treatment of Disseminated Sclerosis, *M. J. Australia* **1** 586 (May 13) 1933.

21 Koch, C. F., and de Savitsch, E. Surgical Treatment of Disseminated Sclerosis by Sympathectomy and Ganglionectomy. Technique by the Anterior Approach, *Brit. M. J.* **1** 1254 (June 11) 1938.

of nicotinic acid without the difficulties, complications and dangers²² incident to these methods

Nicotinic acid when given in proper doses intravenously or intramuscularly produces vasodilatation in the skin of the face, neck, chest and extremities, as has been observed by Smith, Ruffin and Smith,¹³ and subsequently by others²³ and in this series of cases. The readings of skin temperatures, as shown in tables 1 and 2, are the measurable objective evidence of vasodilatation and increased blood velocity in the skin. In view of the pathologic changes of multiple sclerosis centering in the spinal cord and brain, the goal of therapy is to alter or to arrest, if possible, the progress of an existing reversible pathologic process in these tissues.

The evidence presented in this paper that nicotinic acid produces vasodilatation and increased blood flow in the brain and spinal cord is based on the rise of cerebrospinal fluid pressure during the period of flushing of the skin, as shown in figures 1 and 2, and the photographic visualization of dilated vessels and increased capillary filling in the brain and spinal cord of the cat (figs 3, 4, 5, 6 and 7). Elsberg and Hare,²⁴ in their studies on the amyl nitrite test for spinal subarachnoid block, showed that "amyl nitrite, given by inhalation, does produce a definite rise of intracranial pressure, which in an individual with an unobstructed spinal subarachnoid space can be easily measured by a spinal manometer." The rise of intracranial pressure after the inhalation of amyl nitrite is due to the expulsion of cerebrospinal fluid from the cranial cavity incident to an increased volume of the brain brought about by extensive dilatation of the cerebral vessels,²⁵ and in all probability of the spinal vessels as well.²⁴ The rise of cerebrospinal fluid pressure, as observed in cases 1 and 4, following the injection of nicotinic acid and coming on coincidentally with the subjective feeling of warmth and the objective appearance of flushing of the skin, is presumptive evidence of vasodilatation within the brain. The exposed brain and cervicothoracic portion of the cord of the cat showed vaso-

22 Hartman, F. W. Lesions of the Brain Following Fever Therapy. Etiology and Pathogenesis, *J. A. M. A.* **109** 2116 (Dec. 25) 1937. Bennett^{12a} Collins^{12b}

23 (a) Spies, T. D., Cooper, C., and Blankenhorn, M. A. The Use of Nicotinic Acid in the Treatment of Pellagra, *J. A. M. A.* **110** 622 (Feb. 26) 1938. (b) Spies, T. D., Bean, W. B., and Stone, R. E. The Treatment of Subclinical and Classic Pellagra. Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate, with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, *ibid.* **111** 584 (Aug. 13) 1938.

24 Elsberg, C. A., and Hare, C. C. A New and Simplified Manometric Test for the Determination of Spinal Subarachnoid Block by Means of the Inhalation of Nitrite of Amyl, *Bull. Neurol. Inst. New York* **2**:347 (Nov.) 1932.

25 Sollmann, T. A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1936, pp. 479-481.

dilatation both visually and photographically after the intramuscular injection of nicotinic acid, this was most evident at the height of "pinkings" of the cat's tongue and dental mucous membrane and constitutes the direct evidence of an increased blood flow in the brain and spinal cord produced by nicotinic acid

The favorable results obtained in the cases reported may be due in part to the increased oxidation and nutrition of the brain and spinal cord brought about by the improved blood supply. Whether the salutary effect of nicotinic acid is due solely to its effect on the vasculature of the brain and spinal cord or to the possible additional role of nicotinic acid as a vitamin cannot be answered with any degree of certainty within the scope of this paper. Hopkins²⁶ placed nicotinic acid among the essential vitamins and assigned to it the important place of contributing to the complex structure of coenzymes part of the function of which consists of transferring hydrogen to oxygen. Thus nicotinic acid, in its biocatalytic action, may have some influence on the altered molecular state of the diseased nerve tissues in multiple sclerosis.

Although patients with pellagra²⁷ have responded favorably to the use of nicotinic acid as regards nervous and mental symptoms, it cannot be said that nicotinic acid alone was responsible for the effect on the nerve tissue. Spies, Cooper and Blankenhorn^{28a} and Spies and Aring²⁸ have shown that vitamin B₁ deficiency is the factor in pellagra producing the peripheral neuritic phenomena. Lewy²⁹ stated that "the basic factor in most, if not all neuropathies, is a B avitaminosis." Nicotinic acid has been shown by Williams and Spies³⁰ to be part of the vitamin B complex. Deprivation of vitamin B₁ results in disturbance in the normal combustion of carbohydrates and the accumulation of pyruvic acid in the nervous system, both of these deviations from the normal produce significant physiologic and pathologic changes in nerve tissue, and replenishing of vitamin B₁ restores the ability of the nervous system to handle properly pyruvic acid and dextrose.³¹

26 Hopkins, F G. Biological Thought and Chemical Thought, *Lancet* **1** 1201 (May 28) 1938

27 Matthews, R S. Pellagra and Nicotinic Acid, *J A M A* **111** 1148 (Sept 24) 1938. Spies, Bean and Stone^{28b}

28 Spies, T D, and Aring, C D. The Effect of Vitamin B₁ on the Peripheral Neuritis of Pellagra, *J A M A* **110** 1081 (April 2) 1938

29 Lewy, F H. Vitamin B Deficiency and Nervous Diseases, *J Nerv & Ment Dis* **89** 1 (Jan) 1939

30 Williams, R R, and Spies, T B. Vitamin B₁ (Thiamin) and Its Use in Medicine, New York, The Macmillan Company, 1938, p 131

31 Lipschitz, M A, Potter, V R, and Elvehjem, C A. The Metabolism of Pyruvic Acid in Vitamin B₁ Deficiency and in Inanition, *J Biol Chem* **123**: 267 (March) 1938. Hopkins²⁶

Vitamin B₁ was used in conjunction with nicotinic acid in this series of cases, admittedly on an empiric basis. It was felt that whatever effect thiamin chloride may have on diseased nerve tissues, in the light of the foregoing presentation, its effect would be enhanced if it was active at the time vasodilation and improved blood supply were operative during the action of nicotinic acid.

Vitamin B₁ has been used by Stein³² in treatment of a rather impressive list of conditions, among which is included multiple sclerosis. He administered the substance intraspinally and reported encouraging results. To my knowledge, there have been no reports in the literature regarding the use of nicotinic acid in treatment of multiple sclerosis.

In every case in this series in which nicotinic acid-vitamin B₁ therapy was halted for a period there was a return of incapacitating spasticity and incoordination, however, these symptoms were ameliorated within several days, or at most a fortnight, on restitution of treatment. The patients have been the severest judges concerning the relief they experience from the drugs, and in every case they have requested the return to their use after cessation of treatment for a short time.

An important question arises concerning the possible untoward effects of prolonged therapy and the large dose employed—as apparently is necessary in treatment of multiple sclerosis with nicotinic acid and vitamin B₁. It will be seen from the case reports that treatment has been in effect in case 1 since Feb. 15, 1938, in case 2 since March 3, 1938, in case 3 since March 1, 1938, in case 4 since the latter part of April 1938, and in case 5 since May 31, 1938. To date, untoward symptoms have not been encountered, and laboratory and electrocardiographic studies have not shown evidence of harmful effects.

To be sure, complete remissions have not been achieved by the use of nicotinic acid and vitamin B₁ in the cases reported. On the other hand, these cases were instances of advanced multiple sclerosis in which many forms of therapy had been used without appreciably arresting the progress of the disease, in 2 of the cases previous treatment had even aggravated the condition. Every patient noticed improvement in bodily movements and in walking. The patient in case 2 has been restored to her aptitude at the piano and has lost the annoying paraesthesias. Patient 4 is now able to stand and has overcome much of his extreme spasticity. Patient 5 is no longer bedridden and can move his legs, stand while assisted and use his arms, which were previously powerless, for purposes of dressing and eating. It is evident, therefore,

32 Stern, E. L. The Intraspinal (Subarachnoid) Injection of Vitamin B₁ for the Relief of Intractable Pain, and for Inflammatory and Degenerative Diseases of the Central Nervous System, *Am J Surg* 34 495 (March) 1938.

that some improvement has resulted and, what is more significant, a stop has been called to the previous downward course in these cases

What effect nicotinic acid-vitamin B₁ therapy may have in cases of early multiple sclerosis is still to be determined. Further investigation in such cases with both nicotinic acid and vitamin B₁, by use of other modes of administration and other doses, may yield more encouraging results and perhaps throw light on the many blindspots in knowledge of multiple sclerosis

SUMMARY AND CONCLUSIONS

Five cases of advanced multiple sclerosis in which many forms of treatment had been used without appreciably halting the progress of the disease and in which the patients were treated with nicotinic acid and vitamin B₁ are reported

Nicotinic acid produces vasodilatation not only of the skin but also of the brain and spinal cord

Nicotinic acid and vitamin B₁ (thiamin chloride) may be given parenterally in considerable doses (nicotinic acid, 120 mg, thiamin chloride, 33.2 mg) for prolonged periods without apparent harmful effects

Subjective and objective evidence of continued improvement has followed the parenteral use of nicotinic acid and vitamin B₁ in the cases of multiple sclerosis here reported

1813 Delancey Street

DISCUSSION

DR J C YASKIN Several thoughts occur in connection with a presentation of this sort. First, there are two diseases treatment of which is notoriously difficult to evaluate—Parkinson's disease and multiple sclerosis. Second, one knows that multiple sclerosis does have remissions, even when well advanced. Third, a great many patients with multiple sclerosis are easily influenced by suggestion, especially is this true of Dr Moore's second patient, whom, I believe, I saw in the Orthopaedic Hospital. Fourth, some have been using vitamin B₁ in treatment of multiple sclerosis. As a matter of fact, the routine is, when possible, to give fever therapy with the hope that the disease is of virus origin and that some of the organisms may be killed. After this, quinine, liver, liver extract and wine are given when the patients can afford these agents, and I can assure Dr Moore that a number of patients have shown considerable improvement when they have taken vitamin B₁ and liver. Last, although Dr Moore had 1 patient under his observation only a few months, it is a year from the time of beginning the treatment. Although it is difficult to evaluate results, all in all, any one who can suggest something useful in the treatment of multiple sclerosis deserves a great deal of credit.

DR MICHAEL SCOTT I was much interested in Dr Moore's experimental work with nicotinic acid. It was given to 1 patient at Temple University Hospital while on the operating table, and the exposed brain was observed. I did not see any change, however, that was in only 1 case, and only part of the temporal lobe was exposed.

DR A SILVERSTEIN Dr Moore's second patient, I think, went the rounds of every neurologist in Philadelphia. I saw him years ago, he had early signs of multiple sclerosis, but there was such a marked psychogenic overlay that the question of hysteria was considered. He was highly suggestible, and still is. He is now at the Philadelphia Home for Incurables, and is absolutely disabled. If one asks him how he is getting along, he says "I feel fine, as long as I get that injection in me." On the day on which he does not receive an injection he feels sick. I have never seen the man stand. He still has severe spasticity, it all depends on what one means by making a person better. As far as he is concerned, he is disabled. Aside from the upper extremities, he is a cripple. I have seen 4 patients who have objected rather strenuously to this treatment.

DR A ORNSTEIN Does Dr Moore think that the response is due entirely to vasodilatation, to the exclusion of the replacement therapy of avitaminoses?

DR MATTHEW T MOORE I realize fully that in bringing forth any new form of therapy of multiple sclerosis I am embarking on a stormy sea. However, any method or procedure that promises the slightest step forward in treatment of this particularly distressing disease will be of value.

As regards remissions in multiple sclerosis. Many patients do show remissions, but the recent article by Brown and Putnam (*Remissions in Multiple Sclerosis, Arch Neurol & Psychiat* 41:913 [May] 1939) showed clearly, I believe, the statistical evidence regarding remissions and the type of cases in which the remissions occur. They stated that in cases in which the lesions are small, producing such symptoms as diplopia, the probability of remissions is greater and the duration of the remission longer, in cases in which the lesions are large, producing paraplegias and advanced pathologic reflexes, the hope of remission is slight. The part played by suggestion I have, of course, taken into consideration. Any patient with a distressing disease, such as multiple sclerosis, in which the outlook is hopeless is always amenable to wishful thinking, to any hope that can be held out to him, and therefore is highly suggestible.

As I indicated by the lantern slide illustrations, nicotinic acid was used because I believe that if hyperemia similar to that in the skin could be brought about in the nervous system one could dispense with fever therapy and its deleterious effects on nerve tissue. Bennett, Hartman and others have shown that definite pathologic changes may occur in the brain and spinal cord as the result of fever therapy.

The statement that multiple sclerosis may be of virus origin is open to serious question. Pathologically, it is a degenerative disease from the start. As regards the end results in this series. I have been using this therapy for a year and three months in 2 cases and for a year in the remaining 3 cases, in the first 2 cases the improvement has been encouraging, despite the advanced stage of the disease in both.

In reply to Dr Scott regarding the appearance of the brain after the injection of nicotinic acid. The "pinking" of the cerebral cortex is more or less determined by the dose of nicotinic acid. In man, unless 60 mg of nicotinic acid is given as a minimum dose, there may not be any appreciable response.

None of the patients noted a favorable response in less than a week. The spasticity never decreased immediately. The diminution in spasticity was of a subjective character first. There was diminution in spasticity that could be observed objectively later, that this was not due to suggestion was simply shown in case 1 and in case 5, which I did not describe, that of a man who was absolutely bedridden and had not been able to move his body or lower limbs for six months. In two weeks he was able to move his toes, and in three months to undress himself. As regards the mental reaction of the second patient, mentioned by Dr Silverstein, it is true he was suggestible. This man had the most advanced multiple sclerosis I have seen, with pronounced spasticity—so extreme that I was

afraid he had a tumor of the cord extending upward into the foramen magnum, however, careful studies eliminated this possibility. This patient was admitted with extreme spasticity and crossing of the legs. He can now uncross his legs voluntarily and is able to move in bed, which he formerly could not do.

As to Dr. Ornstein's question regarding vasodilatation versus replacement therapy, I have used nicotinic acid on the basis of the effects of vasodilatation, increased oxidation and improved nutrition, which appear concomitantly with increased blood flow in the nervous system. As far as the replacement therapy is concerned, one knows that vitamin B₁ unquestionably plays a role in the degenerative neuropathies, for that reason, the two drugs were used simultaneously to obtain a complementary effect.

EFFECT OF THE RETICULOCYTOGENIC PRINCIPLE IN URINE IN THE TREATMENT OF PERNICIOUS ANEMIA

G E WAKERLIN, M D, P H D

CHICAGO

Normal human urine contains a substance which, like the anti-pernicious anemia principle in liver, is reticulocytogenic for the pigeon, rat and guinea pig¹. An extract of normal human urine prepared by a method basically that used for liver extracts has been found to be reticulocytogenic for the pigeon². Decastello³ reported that normal human urine administered intramuscularly or rectally is effective in the treatment of pernicious anemia, and McCann⁴ found that kidney given by mouth is effective. These findings suggested the possible identity or similarity of the reticulocytogenic principle in urine and the hemopoietic principle in liver. In view of the nonspecificity of the pigeon, rat and guinea pig bioassay methods for the hemopoietic principle in liver, the possibility of urinary excretion of the principle was studied by administering the urine extract previously mentioned orally and intramuscularly to patients with pernicious anemia. A preliminary report of the effect of intramuscular injections of the urine extract in cases of pernicious anemia has been published⁵.

From the Department of Physiology, College of Medicine, University of Illinois, and the Department of Physiology and Pharmacology, University of Louisville School of Medicine

1 Wakerlin, G E, and Bruner, H D. Presence in Normal Human Urine of a Reticulocyte-Stimulating Principle for the Pigeon, *Arch Int Med* **57** 1032 (May) 1936. Liener, G. Ueber antianamisch wirksame Substanzen im Harn, *Wien klin Wchnschr* **48**:559, 1935. Walters, O S. Reticulocytogenic Action of Pernicious Anemia Urine Extracts, *Am J Physiol* **116**:158, 1936.

2 Wakerlin, G E, Bruner, H D, and Kinsman, J M. A Modified Pigeon Method for the Bioassay of Anti-Pernicious Anemia Liver Extracts, *J Pharmacol & Exper Therap* **58**:1, 1936.

3 Decastello, A. Ueber antianamisch wirksame Substanzen im Harn, *Med Klin* **31**:377, 1935.

4 McCann, W S. Effect of Kidney on Blood Regeneration in Pernicious Anemia, *Proc Soc Exper Biol & Med* **25** 255, 1928.

5 Wakerlin, G E. The Relation of the Reticulocytogenic Urine Principle to the Hemopoietic or Antipernicious Anemia Liver Principle, *Am J Physiol* **119**:417, 1937.

METHOD

Urine extract was prepared by concentrating normal human urine to a small volume in vacuo at a temperature of 37 C, adding sufficient 95 per cent alcohol U S P to give a concentration of 70 per cent, concentrating the resulting filtrate in vacuo to a small volume at 37 C, adding sufficient 100 per cent alcohol U S P to give a concentration of 95 per cent and collecting and drying the precipitate. The precipitate derived from 600 cc of urine and equivalent in reticulocytogenic effect on the pigeon to the parenteral liver extract derived from 1,000 Gm of liver was divided into two capsules, which were administered by mouth daily for ten days to each of a group of 3 patients with pernicious anemia. For intramuscular injection the precipitate was dissolved in sufficient physiologic solution of sodium chloride containing 0.5 per cent phenol to give a 1:20 ratio for the

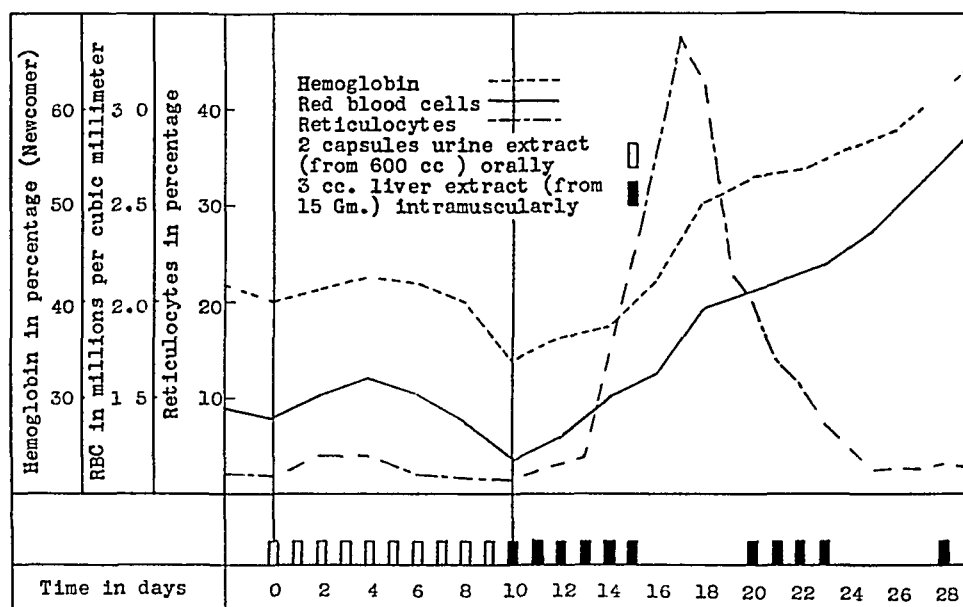


Chart 1—Effect on hemoglobin, red blood cells and reticulocytes of oral administration of urine extract and intramuscular administration of liver extract

volume of the extract and that of the original urine. The urine extract, equivalent in reticulocytogenic effect on the pigeon to a like quantity of two commercial liver extracts derived from 100 Gm of liver, was administered intramuscularly in 3 cc doses daily for ten days to each of a second group of 3 patients with pernicious anemia. Blood counts, except for daily reticulocyte determinations, were made at two to three day intervals before and during treatment with urine extract and during subsequent therapy with liver extract.

RESULTS

In the case of the first patient to receive urine extract by mouth the red blood cell count was 1,400,000 per cubic millimeter. The value for hemoglobin was 68 Gm (Newcomer), the white blood cell count, 4,900 per cubic millimeter,

and the reticulocytes, 22 per cent at the beginning of treatment. The urine extract failed to produce any hematologic or clinical improvement over a ten day period, whereas the subsequent parenteral injection of liver extract resulted in a typical response (chart 1). The other 2 patients were likewise unaffected by the oral administration of urine extract, although subsequent treatment with parenterally administered liver extract was effective.

In the case of the first patient to receive urine extract intramuscularly the red blood cell count was 1,475,000 per cubic millimeter, the value for hemoglobin, 66 Gm (Newcomer), the white blood cell count, 3,700 per cubic millimeter, and the reticulocytes, 02 per cent before treatment. The injections of urine extract were without hematologic or clinical effect during a ten day period. Subsequent treatment with parenterally administered liver extract produced the usual response (chart 2). The other 2 patients similarly showed no improvement with urine

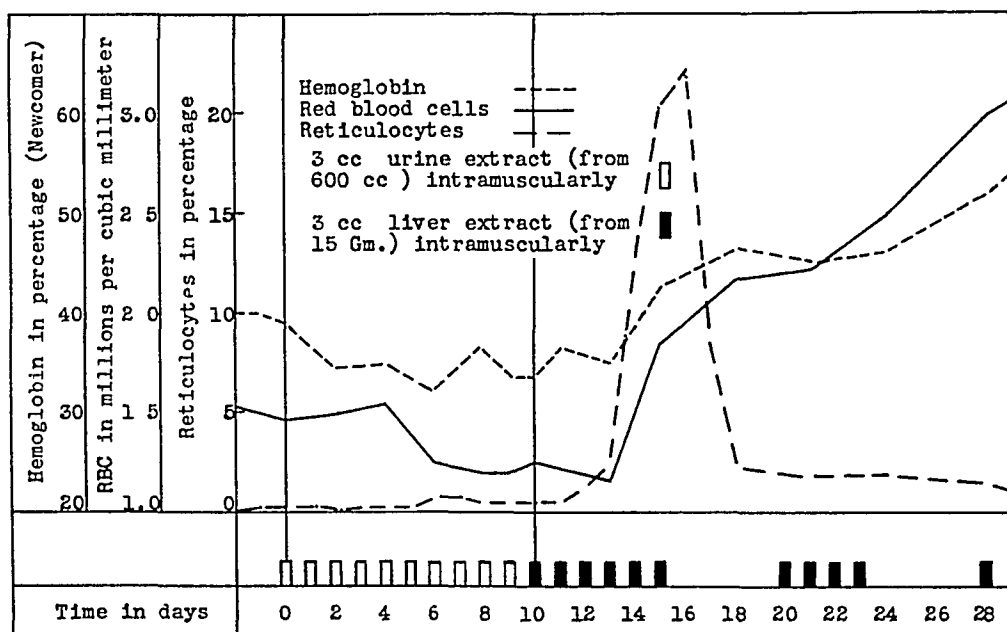


Chart 2—Effect on hemoglobin, red blood cells and reticulocytes of intramuscular administration of urine extract and liver extract

extract given parenterally, whereas liver extract parenterally administered produced a satisfactory response

COMMENT

These results demonstrate conclusively that the anti-pernicious anemia principle in liver is not excreted in significant quantities, if at all, in normal human urine. In terms of reticulocytogenic effect on the pigeon, the amounts of urine extract administered were approximately ten times the therapeutically effective amounts for liver administered orally and intramuscularly, moreover, the urine equivalents used exceeded the amounts of urine reported effective by Decastello³. My previously reported observation on 1 patient, suggesting that urine extract was effective when given intramuscularly in a case of pernicious

anemia,⁶ must be interpreted as due to a coincidental spontaneous remission. Jequier and Apsey⁷ were unable to demonstrate the presence of the hepatic hemopoietic principle in normal human urine administered rectally to a patient with pernicious anemia.

The relation between the reticulocytogenic principle in urine and the hemopoietic principle in liver is obviously an open question. Possibly the urinary principle is a decomposition product or a "building stone" of the hepatic principle. The presence of the urinary reticulocytogenic principle or one indistinguishable from it in the urine of untreated patients with pernicious anemia⁸ does not necessarily speak against the former possibility and is compatible with the latter. The principle in kidney which is effective by oral administration in cases of pernicious anemia may conceivably be an intermediary between the urinary principle and the hepatic principle. Thus, two extracts of kidney⁹ prepared by methods identical with those employed in making liver extracts for parenteral use proved to have a reticulocytogenic potency for the pigeon equal to that of liver extracts but were completely ineffective when given intramuscularly to 2 patients with pernicious anemia.⁵ Dakin, Ungley and West¹⁰ have reported similar findings. In other words, although all three principles are reticulocytogenic for the pigeon, rat and guinea pig, in the treatment of pernicious anemia the hepatic principle is effective orally and parenterally, the renal principle is effective orally but not parenterally, and the urinary principle is effective by neither route. Obviously more work must be done before the interrelations of these three principles, if any, are clarified.

CONCLUSIONS

1 The principle in normal human urine which is reticulocytogenic for the pigeon, rat and guinea pig is not effective orally or intramuscularly in the treatment of pernicious anemia.

2 The anti-pernicious anemia principle in liver is not excreted in demonstrable quantities, if at all, in normal human urine.

6 Wakerlin, G. E. Presence of Anti-Pernicious Anemia Principle in Normal Human Urine, *Proc. Soc. Exper. Biol. & Med.* **32** 1607, 1935.

7 Jequier, E., and Apsey, G. R. M. The Anti-Pernicious Principle. Some Experiments with Urine, *Brit. M. J.* **2** 934, 1938.

8 Wakerlin, G. E. Unpublished data. Jequier and Apsey.⁷

9 The kidney extracts were supplied by the Lederle Laboratories, Inc., Pearl River, N. Y. (Dr. Guy W. Clark), and the Abbott Laboratories, North Chicago (Dr. J. F. Biehn).

10 Dakin, H. D., Ungley, C. C., and West, R. Further Observations on the Chemical Nature of a Hematopoietic Substance Occurring in Liver, *J. Biol. Chem.* **115** 771, 1936.

3 The principle in kidney which is effective by mouth in pernicious anemia is reticulocytogenic for the pigeon but is ineffective when administered intramuscularly to patients with pernicious anemia

4 A clarification of the interrelations of these hepatic, renal and urinary principles should enhance physicians' knowledge of the metabolism of the anti-pernicious anemia principle in liver

Drs Joseph Liebman and H D Bruner assisted in certain phases of this work
Drs R W Keeton and J W Moore made some of the patients available for study

DISSEMINATED LUPUS ERYTHEMATOSUS A CUTA- NEOUS MANIFESTATION OF A SYSTEMIC DISEASE (LIBMAN-SACKS)

REPORT OF A CASE

ARTHUR M GINZLER, MD

AND

T T FOX, MD

NEW YORK

Disseminated lupus erythematosus is a distinctive cutaneous eruption forming part of a systemic disorder that usually includes also characteristic clinical and anatomic evidences of visceral damage. It is now believed that this disorder may occur without its cutaneous manifestation. There exists a considerable body of literature, chiefly dermatologic, in which the clinical aspects of the disease have been well depicted. Though this literature extends back almost seventy years, it is only within the last fifteen years that the present concept of the disease has been evolved and that the visceral lesions observable in most cases have been accurately described.

The chronic forms of lupus erythematosus, whose relation to the disease under discussion has not yet been fully evaluated, have been known since the early part of the last century as localized cutaneous conditions. However, on the basis of the original observations of Kaposi,¹ it has become apparent that with other forms of lupus erythematosus (particularly the acute and subacute disseminated types) there is clinical evidence of an accompanying systemic disease. In some cases the condition pursues an acute, febrile, rapidly progressive course from the onset, soon terminating fatally. In others, the course is less rapid and commonly shows remissions of variable extent. In general, however, the concept has been evolved of a consistent clinical syndrome which permits of the diagnosis, especially in the presence of the cutaneous eruption. Among the more common clinical features, which may be observed in various combinations, are fever, prostration, loss of weight and weakness, changes in the blood (leukopenia, anemia, thrombopenia) and in the urine (albumin, casts, blood), hemorrhagic phenomena (extensive purpura, petechiae with or without pale centers, bleeding

From the Laboratory Division and Medical Service, Hospital for Joint Diseases

1 Kaposi, M. Neue Beiträge zur Kenntnis des Lupus erythematosus, *Arch. f. Dermat. u. Syph.* 4 36, 1872

from mucous membranes), evidence of serous membrane involvement (pleuritis, pericarditis, ascites), severe articular involvement, lymphadenopathy, enlargement of the spleen and abdominal complaints. These different symptoms may vary greatly in severity, any of them may be lacking in an individual case.

The causation of the disease remains unknown. In the past, chiefly tuberculous and streptococcic infections have been incriminated. In our opinion these have now been excluded as specific causes of the disease. There is a tendency at present to regard the disease as a peculiar response, in a constitutionally predisposed person, to a variety of harmful agents. However, the possibility of an as yet undiscovered specific cause cannot be denied.

The evolution of the present concept of this remarkable disease has coincided with the recent advances resulting from detailed gross and microscopic examination of the internal organs, such examinations were seldom made in the earlier cases. The foundation for the present understanding of the disease is deeply rooted in the observations of Libman² on a peculiar type of endocarditis associated with a unique clinical syndrome. The latter, in retrospect, is a pattern of that which may be found in cases of disseminated lupus erythematosus. Indeed, Libman-Sacks disease (as the aforementioned syndrome has come to be called) not infrequently presents, as one of its clinical manifestations, the cutaneous eruption of disseminated lupus erythematosus.

The concept has been further developed by the studies of Baehr³ and of Gross⁴ on Libman-Sacks disease, by those of Baehr, Klemperer and Schiffrin⁵ on disseminated lupus erythematosus and by the later studies of Gross⁶ on the relation between Libman-Sacks disease and disseminated lupus erythematosus.

2 (a) Libman, E. Some General Considerations Concerning Affections of the Heart Valves, *M. Clin. North America* **1** 573 1917, (b) Characterization of Various Forms of Endocarditis, *Tr. A. Am. Physicians* **37** 233, 1922, *J. A. M. A.* **80** 813 (March 24) 1923, (c) Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Tr. A. Am. Physicians* **38** 46, 1923, *Arch. Int. Med.* **33** 701 (June) 1924.

3 Baehr, G. Renal Complications of Endocarditis, *Tr. A. Am. Physicians* **46** 87, 1931.

4 Gross, L. The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol. 2, p. 527.

5 Baehr, G., Klemperer, P., and Schiffrin, A. A Diffuse Disease of the Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis, *Tr. A. Am. Physicians* **50** 139, 1935.

6 Gross, L. Unpublished data, cited by Friedberg, C. K., Gross, L., and Wallach, K. Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, *Arch. Int. Med.* **58** 662 (Oct.) 1936, cited by Libman¹⁴.

We are presenting a detailed report of a case of disseminated lupus erythematosus in which the diagnosis was made clinically and verified by postmortem examination.⁷ Of great interest is the presence of lesions of a distinctive nature in the lymph nodes and the spleen. Their occurrence in the disease has been noted by a few observers, but thus far they have apparently not been considered sufficiently important to warrant a detailed description.

Our case is apparently the first reported in which the characteristic microscopic changes described by Baehni, Klempeier and Schürin⁸ have been demonstrated in a male patient. A notable feature of the disease is its striking predilection for females, indeed, doubt has been expressed as to whether it actually occurs in men. Nevertheless, even if cases without visceral complications are omitted, there remain a number of reports of cases of acute and subacute disseminated lupus erythematosus in male patients, with such characteristic features as a febrile course, anemia and leukopenia, evidence of renal damage and frequently a fatal outcome.⁸ It is true that these reports are open to criticism because of incomplete clinical data and uncertainty about the pathologic changes. However, in the light of the case to be presented it is probable that the cases reported actually did present valid examples of the disease.

7 Ginzler, A., and Fox, T. T. Disseminated Lupus Erythematosus in a Youth, with Some Unusual Findings, *Arch Path* **26** 916 (Oct) 1938.

8 (a) Hardaway, W. A. A Case of Lupus Erythematosus Presenting Unusual Complications, *J Cutan Dis* **7** 447, 1889. (b) Pernet, G. Le lupus érythémateux aigu d'emblée, Thesis, Paris, no. 20, 1908. (c) Kraus, A. and Bohac, C. Bericht über acht Fälle von Lupus erythematosus acutus, *Arch f Dermat u Syph* **93** 117, 1908. (d) Brown, G. A. A Case of Acute Erythematosus Lupus, *New York M J* **106** 931, 1917. (e) Ehrmann, S., and Falkenstein, F. Ueber Lupus Erythematosus, *Arch f Dermat u Syph* **141** 408, 1922. (f) Goeckerman, W. H. Lupus Erythematosus as a Systemic Disease, *J A M A* **80** 542 (Feb 24) 1923. (g) Gibson, R. Fatal Case of Lupus Erythematosus with Post-Mortem, *Brit J Dermat* **37** 232, 1925. (h) Stokes, J. H. Diagnosis of Disseminated Erythematosus Lupus, *M Clin North America* **10** 290, 1926. (i) Clarke, F. B., and Warnock, A. W. Lupus Erythematosus Acutus Disseminatus, *California & West Med* **24** 354, 1926. (j) Brown, C. F., and Bi, Y. W. Lupus Erythematosus. Case Report, *China M J* **42** 775, 1928. (k) Madden, J. F. Acute Disseminated Lupus Erythematosus, *Arch Dermat & Syph* **25** 854 (May) 1932. (l) Lyon, J. M. Acute Lupus Erythematosus, *Am J Dis Child* **45** 572 (March) 1933. (m) Roxburgh, A. C. Acute Disseminated Lupus Erythematosus. Five Fatal Cases, *Brit J Dermat* **45** 95, 1933. (n) Garfield, W. T., Steele, C. W., and Houghton, J. D. Lupus Erythematosus Disseminatus Acutus Haemorrhagicus, *Arch Dermat & Syph* **30** 772 (Dec) 1934. (o) Snapper, I. Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Medes, G. The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935, p. 433. (p) Rose, E., and Golaberg, L. C. The Visceral Lesions of Acute Disseminated Lupus Erythematosus, *M Clin North America* **19** 333, 1935.

REPORT OF CASE

History—H M, a 17 year old youth of Anglo-Scotch origin, with no history of sunburn or abnormal sensitivity to light, was entirely well until Oct 12, 1937, when he noted pain in the right ankle and thought he had sprained it playing baseball. There was no swelling or redness. The next day he experienced a sensation of feverishness and had about half a dozen chills, each lasting five to ten minutes. On successive days he then suffered from aching of both shoulders, swelling and severe pain in both elbow joints, and then swelling and tenderness of the metatarsophalangeal and proximal interphalangeal joints. At this time he was seen by a physician and thought to have rheumatic fever. He felt very weak and was put to bed. After three weeks he felt well enough to go to school, but one week later he collapsed and returned to bed. From this time on (about the middle of November), his temperature varied between 101 and 105 F. During the first week in December a roentgenogram of his teeth revealed abscesses, and two teeth were extracted. Immediately afterward there was a rise in temperature, with chills and sweating. The patient became confined to bed and lost weight and strength continuously. During the last two weeks in December there were generalized aching, tenderness and wasting of muscles, with severe contractures of the elbows and knees. In the last week the knees became very painful, though not red or swollen, and there appeared for the first time a symmetric butterfly-shaped erythematous eruption of the face. The patient was admitted to the Hospital for Joint Diseases Jan 1, 1938, to the medical service of Dr Albert A Epstein, who supplied the clinical data reported here.

Examination—On admission the boy was subacutely ill and very weak and had evidently lost much weight. He was of slender build but entirely masculine in features.

The face presented a symmetric macular erythematous eruption, associated with some scaling, over the flush area. The redness and scaling extended over the eyebrows, and there were slight scaling lesions of the lobes of the ears. The palmar surfaces of the thumbs presented irregular erythematous patches with slight purplish discoloration and rather firm adherent scales in the centers. Similar but smaller lesions were observed on the other finger tips. There were erythematous patches on the knees, and the elbows showed scaling. The mouth presented a marked stomatitis, the mucosa was reddened and covered by numerous small adherent whitish plaques with surrounding reddened zones.

Examination of the heart, lungs and abdomen revealed nothing noteworthy. The blood pressure was 115 systolic and 65 diastolic. The genitalia were normal. Rectal examination revealed a small anal ulcer. The extremities showed evidence of considerable muscular atrophy, and there was marked limitation of extension of the elbows and knees due to the extreme tenderness of the muscles, spasticity and capsular contractures.

Laboratory Data—The urine contained albumin (2 plus), a moderate number of epithelial cells, leukocytes, occasional erythrocytes, and cellular casts.

The blood contained 10.6 Gm of hemoglobin per hundred cubic centimeters (70 per cent) and 3,680,000 erythrocytes and 4,600 leukocytes per cubic millimeter, a smear showed 72 per cent segmented and 5 per cent nonsegmented neutrophilic leukocytes, 21 per cent lymphocytes, and 2 per cent monocytes.

The blood culture and usual agglutination tests of the serum were negative. The agglutination titer of the serum for a strain of hemolytic streptococcus was 1:640. The Kahn reaction was 2 plus, the Wassermann reaction, negative.

The electrocardiogram showed a low T wave in leads I and II and a diphasic T wave in lead IV, which was interpreted as indicating myocardial damage.

Course—During the patient's stay in the hospital his temperature was generally between 100 and 102 F. It was higher in the evening than in the morning, usually varying about 2 degrees daily. Occasionally it went as low as 98 F and as high as 103 F, terminally it rose to 105 F. The urine always contained albumin, varying from a trace to 4 plus, with a tendency toward the larger amounts in the latter stages of the illness. Erythrocytes, leukocytes and granular and hyaline casts were constantly present in the urinary sediment. Repeated blood cultures were sterile. The Frei test gave negative results. The intradermal tuberculin test elicited negative reactions with dilutions of 1:10,000,000 to 1:1,000. The Wassermann reactions varied from negative to 2 plus, the Kahn, from 1 to 4 plus. The positive reactions were regarded as nonspecific. The platelet count at first was 196,000 per cubic millimeter, but later dropped to 92,000. Leukopenia was constant, the leukocyte count varying from 4,100 to 5,800.

On the eighth day after admission the patient experienced a clonic seizure, involving the face and extremities and accompanied by a feeling of dizziness, which lasted for twelve minutes and was followed by nausea and vomiting.

While tachycardia had been practically always present, no murmurs had been heard. Two days after the clonic seizure, a distant to and fro pericardial rub was heard for the first time, about 2.5 cm. inside the left nipple line. An electrocardiogram at this time showed an inverted T wave in leads II and III and a diphasic or upright T wave in lead IV. It was interpreted as indicative of myocardial damage and consistent with a diagnosis of pericarditis.

Four days later the patient had mild diarrhea and complained of abdominal pain. At about this time there was first noted a moderate generalized lymphadenopathy, most marked in the cervical and inguinal nodes but also involving the axillary and epitrochlear nodes. On January 16, two tender erythematous nodules appeared in the right anterior axillary line just above the nipple, they were removed for examination on January 20. Cultures of the excised material remained sterile on all mediums. On histologic examination the nodules proved to be lymph nodes. In addition to follicular hyperplasia and some swelling of the cells of the pulp and the follicular reticulum, there were several areas of cellular necrobiosis involving the pulp adjacent to marginal sinuses and the contiguous capsular tissue. Many of the cells in the affected areas showed swelling and a granular or fibrinous degeneration, with nuclear pyknosis and karyorrhexis. Other cells were completely disintegrated. Silver stains showed relatively little damage to the reticulum fibers in the necrotic areas. The abutting lymphoid tissue showed little monocytic or other reactive inflammation. There was a moderate cellular infiltration of the capsular tissue, predominantly lymphocytic, with a moderate number of plasma cells and a few eosinophils. Staining for bacteria did not reveal any tubercle or other bacilli.

These changes at first suggested the possibility of tularemia, but repeated agglutination tests for it were negative. At this time the histologic changes in the lymph nodes were compared with those recorded in our files for a case of disseminated lupus erythematosus, and their essential similarity was demonstrated. Material from a second group of nodes was injected into guinea pigs, with negative results.

Toward the end of January the facial eruption began to fade, and moderate hypertension (140/90) developed, which was considered all the more significant in view of the marked debility present. Later, petechiae (not white centered) appeared on the finger tips. Abdominal pain recurred. Biopsy of the calf muscle on February 15 revealed no evidence of dermatomyositis or periarteritis nodosa. Meanwhile, the general condition pursued a progressively downhill course. The tachycardia persisted, though after a time the pericardial rub was no longer heard.

Endocardial murmurs were never elicited. The facial eruption continued to fade and finally disappeared, a few weeks before death, with no residual marks or evidence of atrophy. The debility, emaciation, muscle tenderness and joint contractures became steadily worse. Terminally there occurred several convulsive seizures marked by loss of consciousness and clonic movements of the face and right arm. The day before death a bilateral wrist drop developed. Death occurred on March 3, a little less than five months after the onset of the first symptoms.

Gross Observations at Autopsy—Postmortem examination was performed six hours after death. There were marked atrophy of the fatty tissue and the muscles throughout the body, and striking edema of the connective tissues. The lungs showed congestion and edema and an extensive bronchopneumonia. Over the lower lobe of the left lung, away from any area of pneumonia, there was a small patch of fibrinous pleuritis. There was no evidence of recent, old or healed tuberculosis in either the parenchyma or the tracheobronchial lymph nodes. The heart was



Fig 1—Endocardial lesion of right ventricle (hematoxylin and eosin stain, medium power). The section shows an adherent mass of granular material containing nuclei, there are swelling and proliferation of adjacent endothelial cells.

markedly hypertrophied, weighing 490 Gm, with adherent parietal pericardium. The pericardial leaflets were much thickened and completely adherent over their entire extent. No macroscopic valvular, pocket or mural endocardial lesions could be demonstrated. The liver showed only slight fatty change. The spleen was moderately enlarged, weighing 240 Gm, the sections were firm and congested. In addition to follicles of normal prominence, there were numerous scattered pinhead-sized and somewhat larger yellowish areas. The macroscopic appearance resembled that of a tuberculous spleen. The splenic vessels showed no changes. The kidneys showed only a small area of recent infarction in the right kidney, with a thrombosed artery at its apex. The lymph nodes throughout the body—mediastinal, pancreatic, portal, mesenteric, renal and para-aortic—were enlarged some to a marked degree. On section, the majority showed numerous pinhead-sized and larger opaque yellowish areas which might well have been mistaken for tuberculous lesions. Examination of the articular cartilages and synovial tissues of the right knee, which was one of the last joints clinically involved, showed no

gross alterations. Unfortunately, limitation of permission for autopsy precluded examination of the other joints or of the brain, or removal of sections of the affected skin for histologic examination.

Microscopic Observations at Autopsy—Heart. Despite the absence of macroscopic vegetations, histologic study revealed numerous microscopic lesions of the mitral and tricuspid leaflets and the mural endocardium, which were apparently the result of toxic damage to the endothelium. The younger lesions were marked by swelling, proliferation and, frequently, degenerative changes of the lining endothelial cells and slight swelling of the subendothelial tissues. The subendothelial tissue in some areas contained an increased number of cells, many showing nuclear pyknosis and cytoplasmic degeneration, and infiltration by mononuclear cells, young fibroblasts and a few lymphocytes. In one or two there were a few

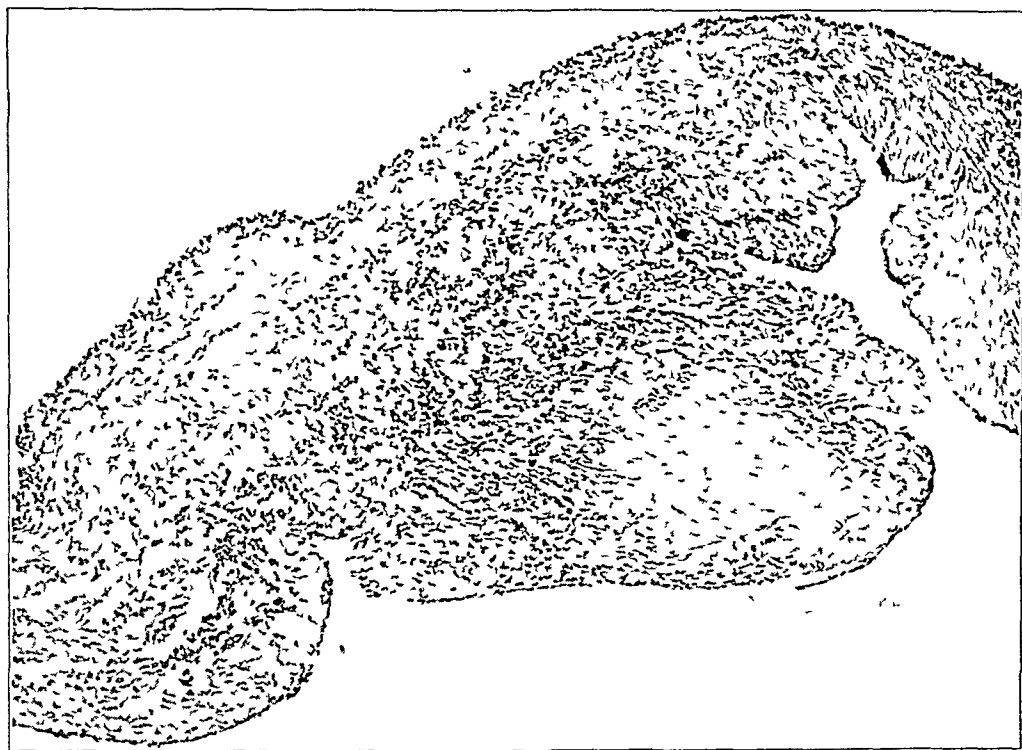


Fig 2—Inflammatory lesion of tricuspid valve

polymorphonuclear leukocytes. In such areas the lining endothelial cells were enlarged and basophilic and contained dark-staining nuclei. One section showed areas of endothelial swelling close to the pocket of the tricuspid leaflet, with adherent masses of pink-staining granular material containing mononuclear cells and numerous dark-staining round or oval nuclei, some of which were pyknotic. The leaflet itself showed a diffuse inflammatory cellular infiltration consisting of polymorphonuclear leukocytes, monocytes, fibroblasts and a few lymphocytes. Many of the cells showed nuclear pyknosis and were difficult to identify. The lining endothelial cells of the valve showed distinct swelling and proliferation. The valve ring was entirely normal. Bacterial stains of the endocardial lesions gave uniformly negative results.

Other than the hypertrophy noted grossly, the myocardium showed no significant changes. Myocardial vascular lesions, Aschoff bodies, Bracht-Waechter lesions and myocardial degenerative changes were not observed. The coronary arteries showed nothing remarkable.

There was pronounced thickening of the pericardium due to a subacute and chronic organizing pericarditis. Some areas were already fibrous and avascular. However, most of the pericardium consisted of inflamed vascular granulation tissue showing considerable fibroblastic proliferation, numerous granulation capillaries with swollen endothelial cells, large numbers of plasma cells, peculiar mononuclear and multinucleated cells and, in places, lymphocytes and polymorphonuclear leukocytes. The latter were especially numerous about areas of fibrinous necrosis. In some places there were large clefts lined by swollen basophilic mesothelial cells.

Kidneys While many of the glomeruli appeared normal, the majority showed distinct changes in some portions, with other portions unaffected. Most of the glomeruli involved were grouped along an interlobular artery. A striking change was an irregular thickening of the basement membrane of many of the capillary

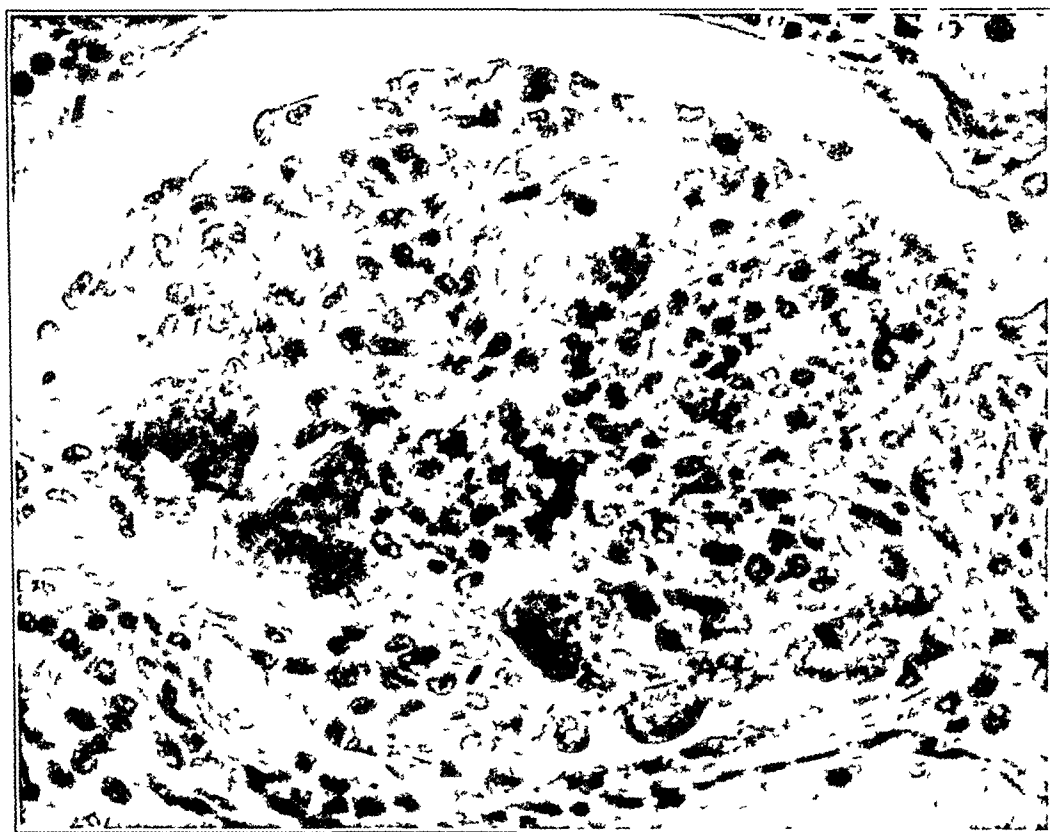


Fig 3—Glomerular lesion (hematoxylin and eosin stain, high power). The section shows extensive degenerative and proliferative changes described in the text (see also figs 4 and 5).

loops, giving rise to the "wire-loop" lesion of Bach, Klemperer and Schiffin⁵. Staining of these lesions for amyloid and lipid gave negative results. Many capillary loops, especially those with thickened walls, contained smooth, pink-staining globules partially or completely obstructing the lumen.

Perhaps even more conspicuous were changes involving the endothelial cells and, to a lesser extent, the visceral epithelial cells of the glomerular tufts. The latter, in places, were considerably swollen. Many revealed a basophilic granular degeneration of the cytoplasm. Their nuclei were sometimes enlarged, bizarrely shaped and hyperchromatic, and sometimes pyknotic. Here and there the tuft was adherent to the glomerular capsule. The endothelial cells showed pronounced

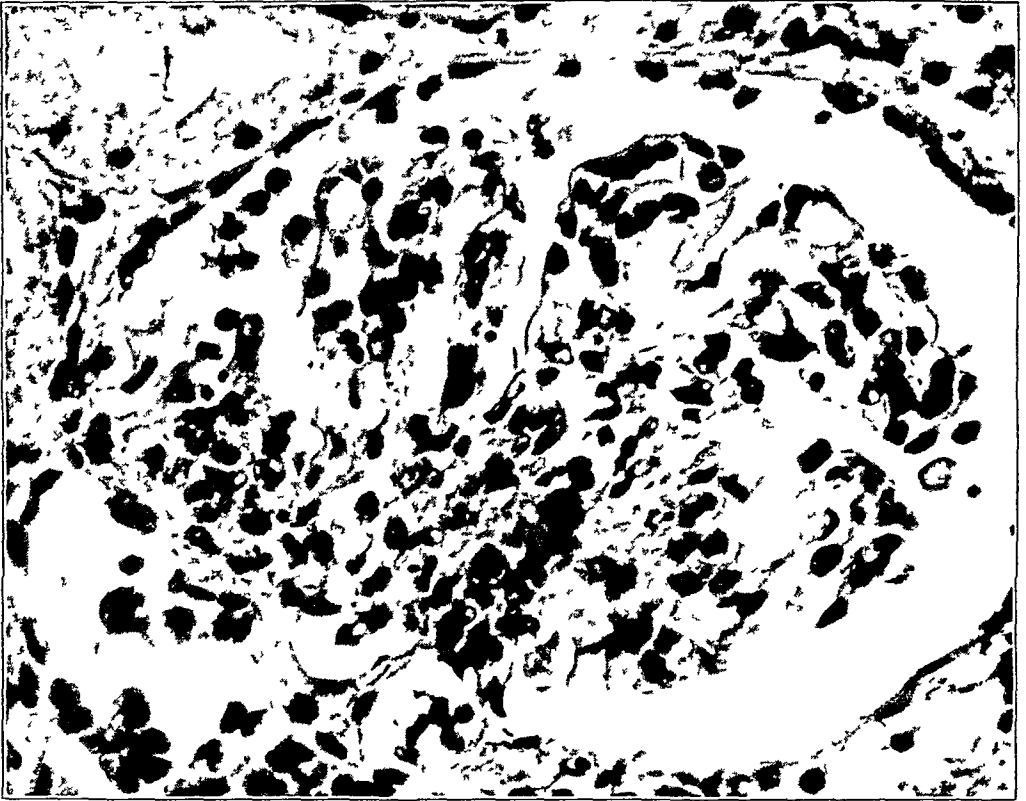


Fig 4—Glomerular lesion (See legend for figure 3)

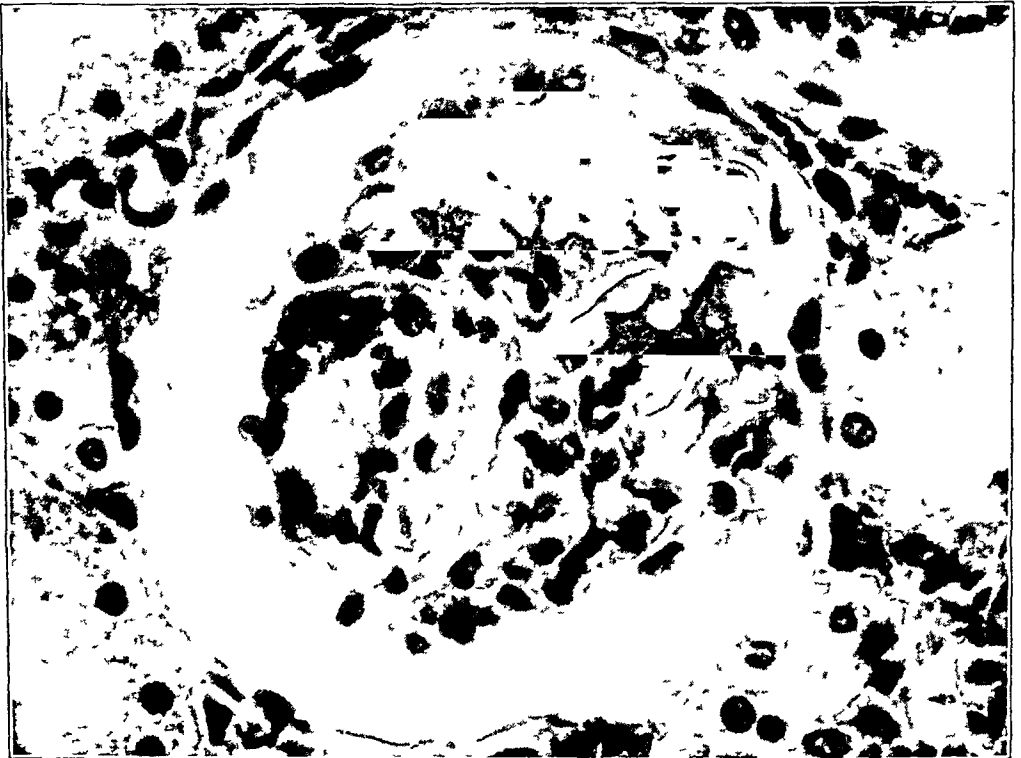


Fig 5—Glomerular lesion (See legend for figure 3)

swelling and proliferation, completely filling some of the loops and contributing to a distinct increase in cellularity of many of the glomeruli. The cells showed occasional hyaline droplet degeneration, but much more severe and extensive were pinkish violet-staining granular degeneration and necrosis of these cells, associated with nuclear pyknosis and karyorrhexis. The changes were often most pronounced at the hilus of the glomerulus. Study led to the conclusion that the formation of the glomerular thrombi was related to the endothelial degenerative changes. This was especially notable in sections stained by the aniline methyl violet method of Weigert, in these both the degenerative cytoplasmic granules and the capillary thrombi (though not the thickened capillary wall) took the violet stain with apparent transitions between

The tubular epithelium showed moderate cloudy swelling and occasional hyaline droplet degeneration. Many tubules contained granular and hyaline casts. No

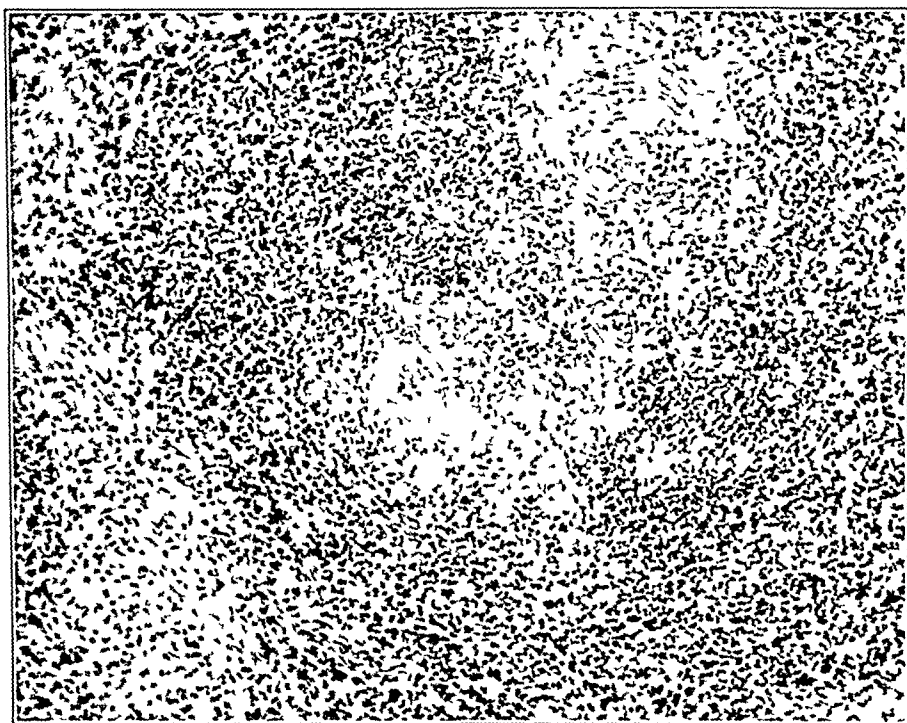


Fig 6—Lymph node. The section shows foci of necrosis.

unusual alterations were observed in the arterioles, arteries and veins. The infarcted area, noted grossly, showed complete necrosis of the tissue with an acute reactive inflammation. A recently thrombosed artery was present at the apex of the infarct, the thrombus most probably originating locally from endothelial damage.

Lymph Nodes. Some lymph nodes showed merely edema, sinus hyperplasia and an inflammatory reaction manifested by the presence of many histiocyte cells and a few plasma and polymorphonuclear cells. Most of the nodes, however, contained numerous areas of necrobiosis apparently in different stages of development. The earliest consisted of foci of cellular necrobiosis with virtually no reactive inflammation. These progressed to larger areas of necrosis with complete cell degeneration and disintegration and nuclear pyknosis and karyorrhexis. Nuclear particles were spread throughout the surrounding pulp which showed marked histiocyte proliferation. Silver stains revealed relatively little damage to the reticulum fibers in the affected areas. In many of these areas some of the affected cells underwent a

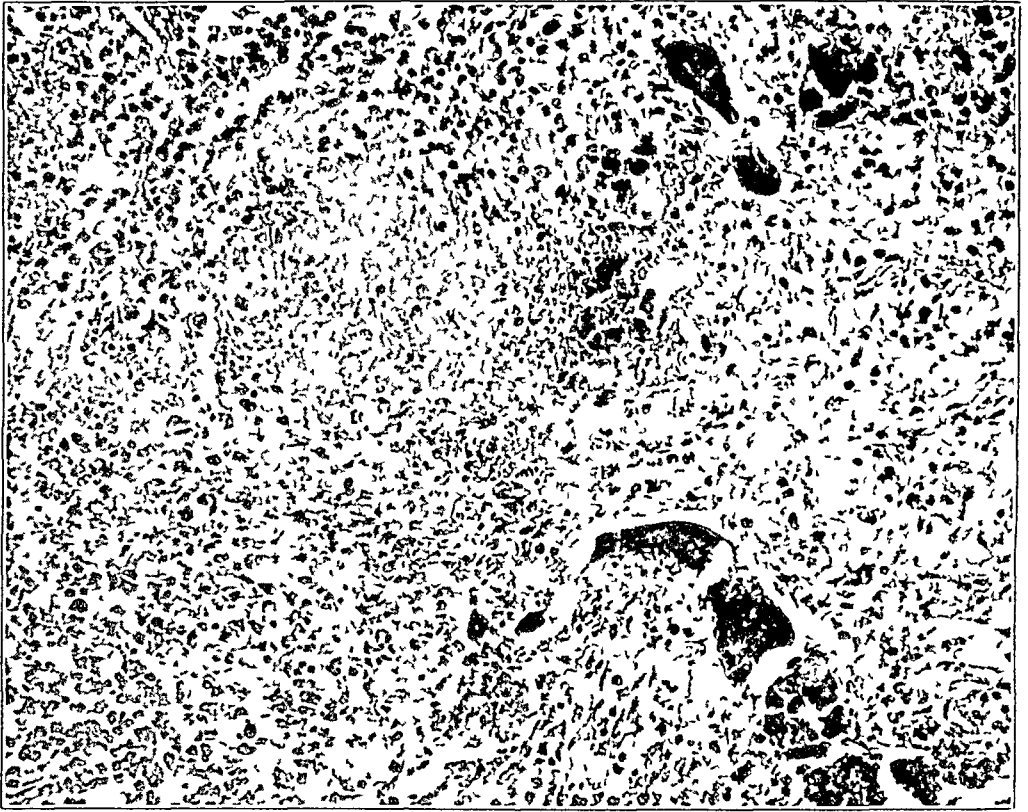


Fig 7—Lymph node The section shows a focal area of necrosis with hematoxylin-staining bodies

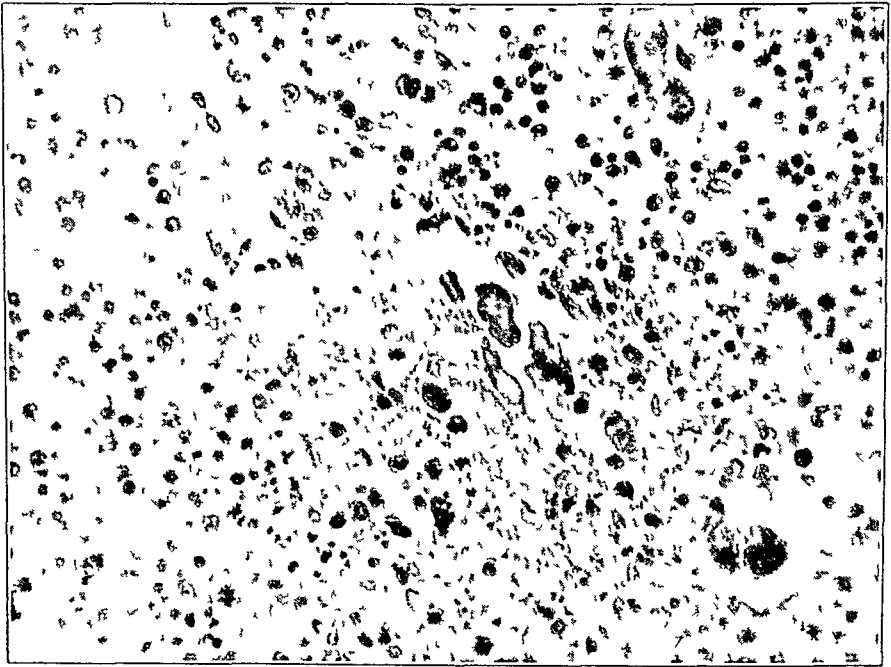
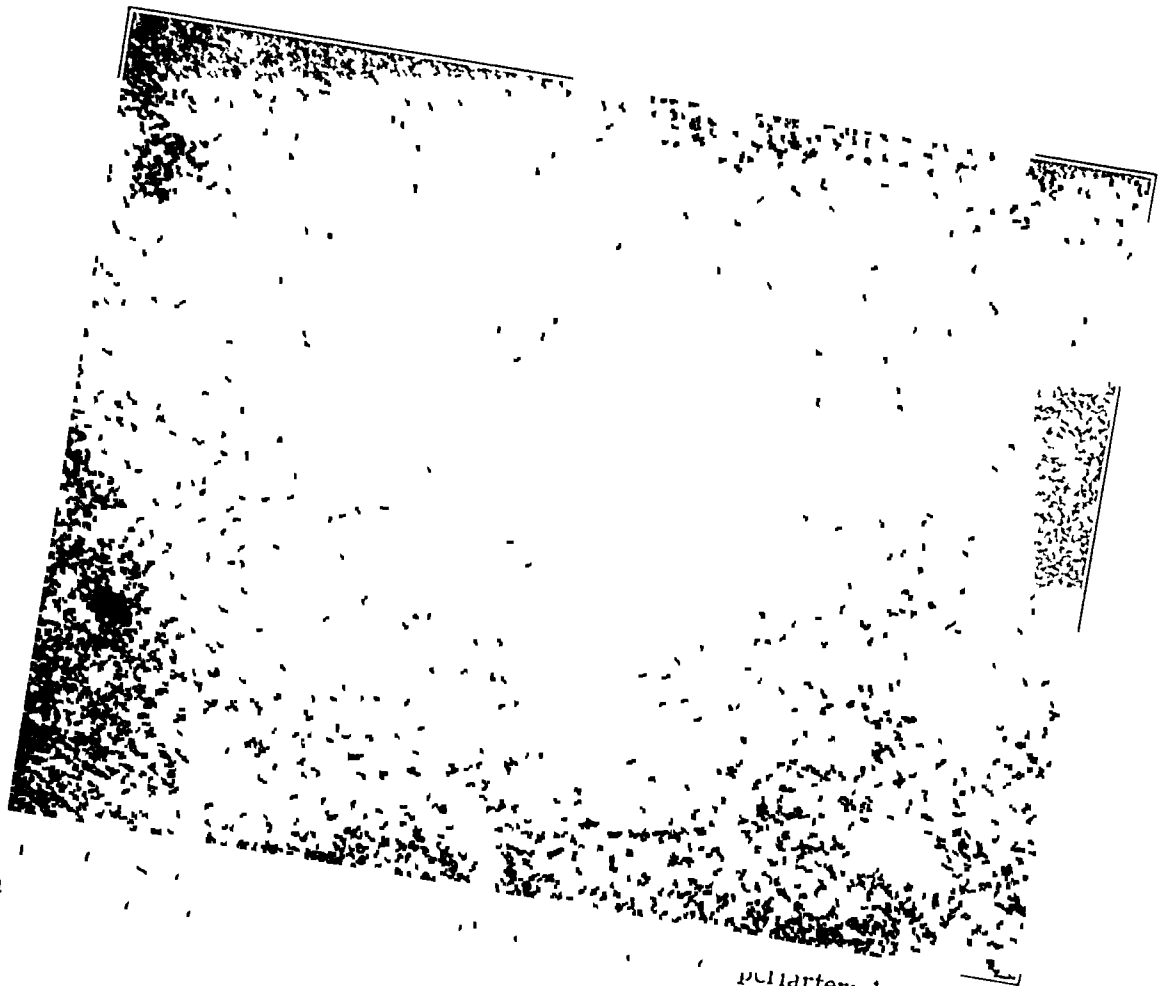


Fig 8—Lymph node The section shows the formation of hematoxylin-staining bodies by coalescence of degenerating cells



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periarterial necrosis of

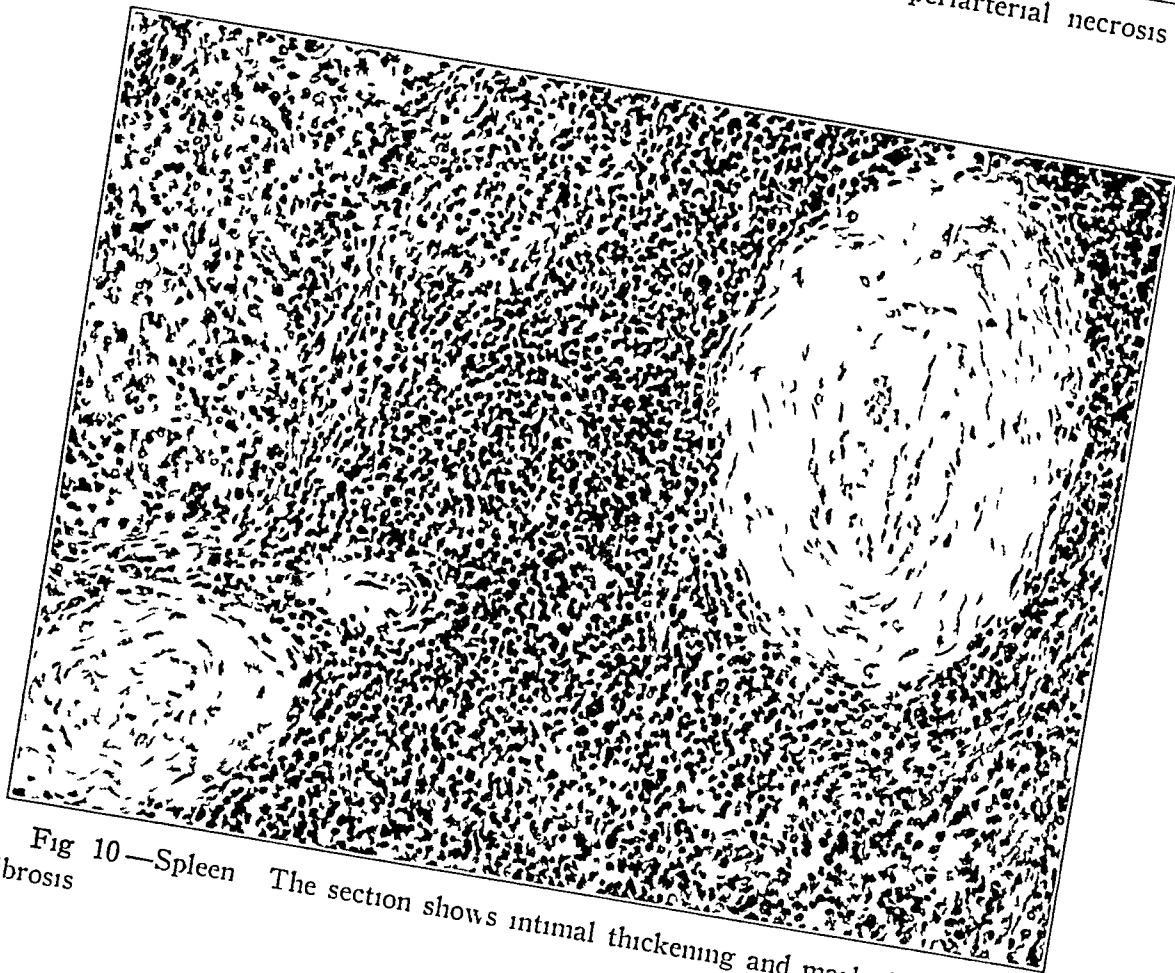


Fig 10—Spleen The section shows intimal thickening and marked periarterial fibrosis

pinkish blue granular degeneration of the cytoplasm with nuclear pyknosis, apparently coalescing to form striking bluish violet-staining masses, resembling calcium, in the hematoxylin-eosin sections. Von Kossa stains, however, revealed no calcium. The surrounding lymphoid tissue showed swelling of the reticulum cells and pronounced swelling and proliferation of the sinus endothelium. In some places there was conspicuous phagocytosis of nuclear particles and of erythrocytes. A small amount of iron pigment was present. In no way did these lesions resemble those of tuberculosis, nor did specific stains reveal any tubercle or other bacilli. Some of the lymph nodes showed strands of fibrosis.

Spleen The most conspicuous change was the presence of numerous areas of necrobiosis of the lymphoid tissue about the follicular arteries. While they closely resembled the lesions in the lymph nodes, these areas in the spleen all represent a similar stage of progression. They consisted essentially of areas of cellular necrosis



Fig 11—Vascular lesion in cortex of rib. The section shows marked thickening of the capillary wall. There is "creeping" replacement of adjacent osseous tissue.

with nuclear pyknosis and karyorrhexis and little damage to the reticulum fibers. There was no noteworthy reactive inflammation except for the occasional presence of mononuclear histiocytic cells. The arteries of the follicle showed conspicuous adventitial fibrosis and, in places, intimal proliferation.

The pulp revealed marked engorgement of the intersinusoidal cords, most of the sinuses being empty of blood and the sinus endothelium conspicuous. The red pulp was not involved in the areas of necrosis. There was no significant inflammatory reaction. A fair amount of intracellular iron pigment could be demonstrated.

Lungs Sections showed edema and an extensive patchy bronchopneumonia, not unusual in character. In one section there was an area of swelling, proliferation, and marked degeneration of the lining mesothelial cells and pleural connective tissue. The pleura was covered by a thin film of fibrin. Other than these, the lungs showed no noteworthy changes. In particular, no vascular alterations were noted.

Osseous System Sections of red marrow showed definite hypoplasia of the blood-forming elements, though all were present in normal proportions. There were pronounced capillary engorgement and edema of the fatty marrow, such as are often observed in debilitating diseases. The marrow revealed no vascular alterations or areas of necrosis. In the bone cortices, however, especially of the ribs, many of the capillaries presented a very striking thickening of their walls.

Knee Sections of the synovial tissues and articular cartilages of the right knee showed surprisingly little change. In places there was slight hyperplasia of the synovial lining cells and at one point a small bit of fibrin covered the surface. The sublining synovial tissues showed no inflammatory or vascular alterations.

Blood Vessels In addition to the abnormalities noted heretofore there were distinct dilatation and thickening of the capillaries throughout the connective tissues of the body. Furthermore, a number of small vessels showed partial thrombosis and organization.

Other Tissues Changes elsewhere were not conspicuous. A section of skin taken from an erythematous area of the thumb showed marked capillary dilatation but no thrombosis or hemorrhage. There were no significant dermal or epidermal changes. Unfortunately, limitation of the permission for autopsy prohibited removal of other affected areas of skin. Sections of voluntary muscle showed atrophy, irregular degenerative changes of the muscle fibers and occasional mild interstitial inflammation. The liver, pancreas, adrenals, bladder, seminal vesicles and testes showed no significant changes.

COMMENT ON CASE

Aside from the unusual occurrence of the disease in a male subject, a review of the clinical data in this case elicits a number of points of interest which are important because of their not infrequent occurrence and consequent significance in regard to disseminated lupus erythematosus: (1) onset with polyarthralgia, (2) exacerbation of symptoms following removal of focus of infection, (3) appearance of a butterfly-shaped erythematous facial eruption two months after the onset of symptoms, (4) febrile course with clinical evidence of pericarditis (accompanied by electrocardiographic changes), renal damage, depression of bone marrow function (leukopenia, anemia, thrombopenia) and nontuberculous lymphadenopathy, (5) tachycardia, (6) elevation of blood pressure, (7) negative tuberculin and Fieci tests, repeatedly negative blood cultures and negative serologic tests for typhoid and paratyphoid fevers, undulant fever and tularemia, (8) nonspecific serologic reactions for syphilis, (9) disappearance of the facial eruption, leaving no atrophy or other residua, with fatal progression of the disease.

There was no history of unusual photosensitivity, so frequently present in cases of acute disseminated lupus erythematosus. Petechiae were observed, but, as Libman has pointed out, caution must be exercised in interpreting their significance when they are found in or close to areas of skin affected by the disease.

The final diagnosis was arrived at with some difficulty, though it was considered from the time of admission. Erythematous rashes of the type

present in this case and progressive renal damage do not typically occur in rheumatic fever, nor was there other clinical evidence to substantiate that diagnosis. Pericarditis seldom occurs as part of subacute bacterial endocarditis, and repeated cultures failed to reveal any organism in the blood of this patient. A diagnosis of typhoid or paratyphoid fever, undulant fever or tularemia could not be sustained in the presence of negative serum agglutination tests. The Frei and tuberculin tests were negative. Biopsy failed to reveal the presence of periaortitis nodosa. In the absence, then, of any other definite etiologic factors, the combination of a febrile illness with an erythematous facial eruption, together with arthralgia, pericarditis, negative blood cultures and evidence of renal damage and bone marrow depression, seemed definitely to point to disseminated lupus erythematosus of the systemic type. The fact that a biopsy revealed nontuberculous lymph node lesions of the type seen in undoubted cases of the disease definitely confirmed this diagnosis.

Grossly, no conspicuous changes, aside from the bronchopneumonia (evidently terminal) and cardiac hypertrophy and pericarditis, were noted at autopsy. However, microscopic study revealed widespread lesions involving the vascular system (particularly the renal glomeruli), heart, lymph nodes and spleen.

The glomerular lesions were essentially of the type described first by Baehr, Klemperer and Schiffin⁵ and later by Klemperer in the case reported by Denzer and Blumenthal.⁹ As Klemperer pointed out, these glomerular alterations are distinctly unusual. They do not resemble those found in the glomerulitis in general infections described by Bell¹⁰ or in glomerulonephritis. It is probable that the development of the glomerular changes is analogous to that of the endocardial changes to be described, thus one of the most characteristic pathologic changes in this disease is represented by a process of endothelial and mesothelial swelling, proliferation, degeneration, necrosis and reactive inflammation.

The changes in the heart bore no resemblance to those of rheumatic heart disease, nor did they appear to be of bacterial origin. Our study of the endocardial lesions led us to believe that they were essentially of the type described by Gross^{4, 6} in studies of Libman-Sacks disease with and without lupus erythematosus and of disseminated lupus erythematosus with and without atypical verrucous endocarditis. Other cases of disseminated lupus erythematosus with endocardial lesions probably related to but not identical with those described by Libman and Sacks

9 Denzer, B. S., and Blumenthal, S. Acute Lupus Erythematosus Disseminatus, *Am J Dis Child* **53** 525 (Feb) 1937.

10 Bell, E. T. The Early Stages of Glomerulonephritis, *Am J Path* **12** 801, 1936.

have been reported by Peinet,^{8b} Belote and Ratner,¹¹ Jarcho,¹² Rose and Goldberg,^{8p} Weidman and Gilman¹³ and others

The microscopic endocardial changes undoubtedly serve as the basis for the subsequent development of the gross verrucous lesions, though it is possible that such microscopic lesions may heal. Indeed, the possibility of healing of atypical verrucous endocarditis has been considered by Libman^{2c, 14}. The appearance of these changes in the heart suggests that the initiating factor is damage to the endocardial lining by an as yet unascertained toxic agent. This primary involvement of the endothelium is clearly brought out in the studies of Gross,⁶ it differs from the mode of attack in rheumatic fever, in which the endothelial changes are secondary to inflammatory involvement of the valve rings and valves. The pathogenesis of the pericarditis appears to be essentially similar. Libman has pointed out that the gross lesions in atypical verrucous endocarditis may be slight or extensive. The occurrence of microscopic lesions in the absence of gross vegetations indicates the necessity for detailed histologic study, just as does the occurrence of extensive glomerular changes in the absence of gross scarring or hemorrhage of the kidneys. In addition to the characteristic endocardial changes, a terminal nonbacterial thrombotic endocarditis may be found in this disease, as in many others^{11a}.

The occurrence of the focal necrotic lesions in the lymph nodes has been mentioned,¹⁵ but we have not found a detailed description of them. They appear to be as characteristic as the glomerular changes, though undoubtedly of less frequent occurrence. Short¹⁶ in 1907 reported a fatal case of lupus erythematosus in a 28 year old woman in which the lymph nodes showed areas of necrosis with no micro-organisms present. The development of clinical lymphadenopathy in cases of disseminated lupus erythematosus has long been noted¹⁵ and has frequently been

11 Belote, G. H., and Ratner, H. S. V. The So-Called Libman-Sacks Syndrome. Its Relation to Dermatology, *Arch. Dermat. & Syph.* **33** 642 (April) 1936.

12 Jarcho, S. Lupus Erythematosus Associated with Visceral Vascular Lesions, *Bull. Johns Hopkins Hosp.* **59** 262, 1936.

13 Weidman, F. D., and Gilman, R. L. A Case of Acute Disseminated Lupus Erythematosus, *Brit. J. Dermat.* **43** 641, 1931.

14 Libman, E. The Varieties of Endocarditis and Their Clinical Significance, *Tr. A. Am. Physicians* **53** 345, 1938.

14a Friedberg, C. K., Gross, L., and Wallach, K. Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, *Arch. Int. Med.* **58** 662 (Oct.) 1936.

15 Keil, H. Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, *Arch. Dermat. & Syph.* **36** 729 (Oct.) 1937.

16 Short, T. S. Fatal Case of Acute Lupus Erythematosus, *Brit. J. Dermat.* **19** 271, 1907.

cited as evidence of the tuberculous nature of the disease¹⁷ Microscopic examination, however, may disclose the nontuberculous nature of the changes in some cases Thus Roberts¹⁸ reported a fatal case of acute disseminated lupus erythematosus in a 21 year old woman in which the mesenteric nodes had been considered as the seat of old caseous tuberculosis and some of the other glands as showing recent tuberculosis but microscopic study failed to reveal any evidence of tubercles or of tubercle bacilli In our case the histologic structure of the lesions in the lymph nodes was in no way suggestive of tuberculosis, nor did specific search reveal any tubercle or other bacilli The prevailing belief that tuberculosis is not a specific etiologic factor in the disease was thus substantiated

Areas of focal necrosis have been noted also in the spleen (Snappei,²⁰ Jarcho¹²) though not described in detail They too appear to be a characteristic manifestation and are not tuberculous in structure The perivascular fibrosis of the smaller arteries of the spleen has been described by Libman and Sacks²¹ in one of their cases, and by Klemperer in the case of acute disseminated lupus erythematosus reported by Denzer and Blumenthal⁹

It is interesting that the synovial tissues of the knee joint presented few significant changes, in spite of the prominence of the arthritic symptoms, which are so frequently present in this disease It is of course possible that in this case and in other cases other articular tissues might have shown more pronounced changes

It is unfortunate that limitation of permission for autopsy precluded examination of the brain, since cerebral symptoms similar to those present in our case are not infrequently noted in fatal cases of the disease They were present in such a case previously studied in this hospital Jarcho¹² has described the occurrence in 1 of his cases of multiple small areas of encephalomalacia and of thrombi in many of the small cerebral vessels

Finally, we note the observation of Klemperer¹⁹ that in some cases in which the disease was acute and rapidly fatal no morphologic changes could be found in the internal organs Such cases are indeed few and possibly are found only when the toxic process is so virulent as to produce death after an interval insufficient for the production of visible anatomic changes

17 Keil, H Relationship Between Lupus Erythematosus and Tuberculosis A Critical Review Based on Observations at Necropsy, *Arch Dermat & Syph* **28** 765 (Dec) 1933

18 Roberts, L Acute Lupus Erythematosus (*Aigu d'Emblée*), *Brit J Dermat* **23** 167, 1911

19 Klemperer, P, in discussion on Ginzler and Fox⁷

REVIEW OF OTHER CASES

Lupus erythematosus was first described in the early part of the last century, by Bielt, Hebra and Cazenave, as a local cutaneous disease of no prognostic concern. In a brief report in 1869 and in his classic paper of 1872, Kaposi¹ classified this dermatosis into two forms: lupus erythematosus discoides and lupus erythematosus discretus et aggregatus. He described cases, particularly of the latter type, in which the disease, unlike the ordinary chronic forms, presented evidence of grave visceral complications. The symptoms were sometimes accompanied by an erysipelas-like eruption of the face, to which he referred as erysipelas perstans faciei. The disease pursued an acute or subacute febrile course with severe toxic manifestations. In addition, Kaposi noted the occurrence of arthritis, pleuropulmonary complications and lymphadenopathy. Three of his series of 11 patients died while under observation.

After Kaposi's original contribution, similar observations were reported from time to time. The clinical picture, as described in these reports and in the dermatologic texts of the period, varied little from that recorded by Kaposi except that the frequent occurrence of renal damage was noted. In 1908 Pernet^{8b} wrote his well known monograph based on 9 cases from the literature and a tenth case of his own. Pernet, however, included only cases in which the disease was acute from onset and rapidly fatal, a syndrome which he called *lupus érythémateux aigu d'emblée*. He felt that these cases formed a group separate and distinct from those in which the course was subacute, or those in which the course was acute and albuminuria was present. Such distinctions, however, do not appear to be justified, and these cases probably do not differ in nature from the cases with a subacute course or those in which there is an acute exacerbation of a chronic form of lupus erythematosus, which may have the same grave features and eventual fatal termination.

The literature for a half-century following Kaposi's report added little to knowledge of the nature and pathogenesis of the disease. During this time, particularly in the Continental literature, the disease was generally held to be of tuberculous nature, on what seems rather meager evidence. Perhaps for this reason the available pathologic material appears to have been inadequately studied, so that until recently no characteristic visceral pathologic changes had been described in detail. An exception, perhaps, is a description of the renal glomeruli by Keith and Rowntree²⁰ in a case of lupus erythematosus in a 20 year old woman; the renal lesions were misinterpreted, however, as those of an ordinary chronic glomerulonephritis.

20 Keith, N. M., and Rowntree, L. G. A Study of the Renal Complications of Disseminated Lupus Erythematosus, *Tr. A. Am. Physicians* 37: 487, 1922.

Indeed the disease seems to have been known chiefly to dermatologists, who, it must be said, were familiar not only with the ordinary discoid type of lupus erythematosus but also with the more uncommon forms with systemic involvement, as may be seen from a perusal of the proceedings of dermatologic societies. It is not improbable, however, that patients with this disease were often seen by internists, particularly when the dermatologic manifestations were not prominent, and treated as patients with typhoid fever, rheumatic fever, scarlet fever, erysipelas, arthritis, pellagra or acute abdominal disease. Nevertheless, Keefer and Felty,²¹ in 1924, described 3 cases of the disease brought to their attention for reasons other than the cutaneous manifestations, they stated the belief, after a study of their cases and those reported in the literature, that the disease was a definite clinical entity "occurring nearly always in females and characterized by fever, joint and muscle pains with swelling but without joint changes, abdominal pains, glandular enlargement sometimes associated with splenomegaly, typical disseminated skin lesions with great prostration, occasionally with delirium, secondary anemia often with normal leukocyte count, a downhill course with increasing asthenia and generally failure, and finally, exitus due to an intercurrent respiratory infection or to nephritis." They believed that the pathologic findings were neither constant nor characteristic, and that the lesions of pneumonia and nephritis, often present, could not be regarded as playing a primary role. Essentially similar conclusions were arrived at by Goeckerman,^{8b} Mook, Weiss and Bromberg²² and Madden.^{8k}

As previously stated, the basis for the present understanding of the nature of this remarkable disease rests to a large extent on the observations of Libman.² In his studies of endocarditis he encountered a series of cases (including 1 case observed as early as 1911) in which, though showing similarities to both rheumatic and subacute bacterial endocarditis, the disease differed in certain fundamental respects from each, clinically and pathologically. In 1924 Libman and Sacks^{2c} reported in detail, as instances of a clinical-pathologic entity, 4 cases of this disease in which the endocardial lesions were denoted as atypical verrucous endocarditis, this syndrome has come to be known as Libman-Sacks disease. Clinically the condition in these cases formed a well defined complex which the authors summarized as follows: "The disease in the form in which it attacked young people who had previously had no organic symptoms ran a subacute course with fever and progressive

21 Keefer, C. S., and Felty, A. R. Acute Disseminated Lupus Erythematosus, *Bull. Johns Hopkins Hosp.* **35** 294, 1924.

22 Mook, W. H., Weiss, R. S., and Bromberg, L. K. Lupus Erythematosus Disseminatus, *Arch. Dermat. & Syph.* **24** 786 (Nov.) 1931.

anemia Briefly enumerated, the findings were pericarditis, white-centered petechiae, arthritis, erythematous and purpuric rashes, ulcerative lesions of the mucous membranes, pleuro-pulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia, and repeatedly negative blood cultures Two of the patients had an eruption of the face which resembled acute lupus erythematosus disseminatus" The authors emphasized the inconsistency of a diagnosis of rheumatic endocarditis when white-centered petechiae and glomerulonephritis were present, and, similarly, of a diagnosis of subacute bacterial endocarditis when erythematous rashes, pericarditis, and repeatedly negative blood cultures were present

Pathologically, in the 4 cases verrucous endocardial vegetations were observed which differed in structure and localization from those in both rheumatic and subacute bacterial endocarditis The lesions contained no bacteria Aschoff bodies and Biacht-Waechter lesions were not found There was a nonbacterial organizing pericarditis In 2 cases there was diffuse glomerulonephritis, in 3 pleuritis, in 2 bronchopneumonia, in 1 ascites and in 3 enlargement of the spleen together with small splenic infarcts, in 1, microscopic examination revealed periarterial hyaline thickening in the spleen The authors felt that the etiologic agent (whatever it might be) or its toxin had a great affinity for the glomerular endothelium In 1925, on clinical grounds, Libman advanced the hypothesis that endocarditis is not an essential feature of the disease

Gross⁴ described in great detail the cardiac changes in 11 cases of atypical verrucous endocarditis Of particular importance was the occurrence in 5 of the patients, all female, of an erythematous eruption having the appearance of acute lupus erythematosus The 11 cases included the 4 of Libman and Sacks, in 2 of which the eruption was noted Both Libman and Sacks and Gross recognized the possible significance of this symptom

In 1931, in a report on renal complications in 17 cases of Libman-Sacks disease, Baehr³ concluded that the disease is an expression of a systemic process affecting the capillaries and finer ramifications of the vascular tree, in which toxic damage produces swelling, proliferation and necrosis of the vascular endothelium Significantly, because of 2 additional cases in which no endocardial lesions were present, Baehr stated the opinion that endocarditis is not an essential feature of the disease, and may be absent in cases in which one finds the typical changes in the skin, kidneys and other viscera

An important advance was made in 1935 by Baehr, Klempeier and Schiffin⁵ They summarized the clinical and pathologic findings in a series of cases which presented the complete clinical picture, including

the cutaneous lesions, of disseminated lupus erythematosus. Of particular importance is their description of the peculiar vascular lesions, and especially the glomerular lesions which, when present, are so characteristic. They summarized the clinical course as "characterized by a more or less prolonged, irregular fever with a tendency to remissions of variable duration, by involvement of synovial and serous membranes, by depression of bone-marrow function and by clinical evidences of vascular alterations in the skin, the kidneys and the other viscera. The disease often ends fatally after a period varying from four weeks to five years." Twenty-two of their 23 subjects were females, in the case of the 1 male patient the diagnosis was made on the basis of an atypical erythema of the face, and was considered to be doubtful.

Pathologically, there was evidence of pleuritis, pericarditis or both in 17 cases. A coarse nonrheumatic, nonbacterial verrucous endocarditis was present in 13 cases, in 5 of which it conformed exactly to the picture of atypical verrucous endocarditis in Libman-Sacks disease. Aschoff bodies were not found. Tuberculosis was absent in all but 2 cases, in 1 a single caseous tracheobronchial lymph node was observed and in the other there was terminal miliary tuberculosis after more than a year of debilitating illness. Remarkable vascular lesions were revealed microscopically throughout the finer ramifications of the systemic and sometimes also the pulmonary circulation. These consisted of (1) simple dilatation of the capillary bed in certain areas, as in the skin, with bloody and serous extravasations, (2) proliferative lesions of the lining endothelium of capillaries, arterioles and venules, associated with thrombi which often obstructed or occluded the lumen, and (3) degenerative and necrotizing lesions in the wall of such vessels, associated with thrombosis and sometimes with hemorrhage into the adjacent tissues.

Glomerular changes, consisting of proliferative and thrombotic lesions of the capillary loops, were conspicuous in most cases. In particular the authors noted a peculiar hyaline thickening of the capillary walls which they called the "wire-loop" lesion. This lesion had not been seen by them in any other human disease and was approached only in eclampsia. The authors stated the belief that these patients had been suffering from a peculiar constitutional reaction to a low grade infection, and that the disease was not conditioned by the nature or severity of the local infection or intoxication but seemed rather to depend on some peculiarity in the constitutional reaction of the host. It is important to emphasize here that Libman, as well as Baehr, Klemperer and Schiffrin, observed cases indicating that essentially the identical disease may occur in subjects in whom the cutaneous eruption never develops.

Comparison of the clinical and pathologic details observed in cases of disseminated lupus erythematosus, on the one hand, and of atypical verrucous endocarditis on the other, and study of the conclusions as to the essential nature of the process in the two diseases clearly indicate that they are closely related if not actually identical. Gross⁶ compared the cardiac lesions in 23 cases of disseminated lupus erythematosus with those in 4 cases of Libman-Sacks disease without lupus erythematosus. In the former group, he noted macroscopic lesions in 9 cases and microscopic lesions in most cases, with few exceptions, he considered these lesions to be characteristic of the group and in many instances identical with the lesions found in the cases of atypical verrucous endocarditis. Gross concluded that the two diseases are essentially the same and should be placed in the single category of Libman-Sacks disease. We believe it is likely that the condition classified by Friedberg, Gross and Wallach^{14a} as nonbacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions also belongs in this category. Indeed, we are informed that a reexamination of the cases of this condition has disclosed the characteristic lesions in 3 of the cases, in the fourth, insufficient material remains available.²⁴

Other cases that undoubtedly are also instances of this disease have been reported in recent years by Tremaine²⁵ and by Christian,²⁶ similarly under somewhat obscure titles. Nevertheless, that there is a growing appreciation of the essential similarity of the syndromes in spite of some variations in symptoms is evidenced in a recent paper by the Reifenssteins²⁷ in which an excellent selection of cases from the literature is described.

In regard to the etiology of the disease there is little to offer save conjecture. As we have indicated, the evidence in favor of tuberculosis as a specific causative factor is unconvincing. It rests on the occasional association of the disease with tubercle bacilli, the presence of scrofulous

23 Footnote deleted

24 Friedberg, C. K. Personal communication to the authors

25 Tremaine, M. J. Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis, *New England J. Med.* **211** 754, 1934

26 Christian, H. A. Long-Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis. A Clinical Syndrome of Unknown Etiology, *M. Clin. North America* **18** 1023, 1935

27 Reifensstein, E. C., Reifensstein, E. C., Jr., and Reifensstein, G. H. A Variable Symptom Complex of Undetermined Etiology with Fatal Termination, Including Conditions Described as Visceral Erythema Group (Osler), Disseminated Lupus Erythematosus, Atypical Verrucous Endocarditis (Libman-Sacks), Fever of Unknown Origin (Christian) and Diffuse Peripheral Vascular Disease (Baehr and Others), *Arch. Int. Med.* **63** 553 (March) 1939

stigmas of clinically diagnosed tuberculosis, a family history of tuberculosis and the occasional demonstration at autopsy of tuberculosis, especially of the lymphatic type. The last, as we have shown, is especially open to doubt unless the diagnosis is verified by microscopic study, since the changes in the lymph nodes and spleen may simulate, especially grossly, those of tuberculosis. Certainly there is no doubt that in many cases, including the case we report here, careful search has failed to reveal any evidence of tuberculosis. The evidence that the disease is of streptococcic origin is even less convincing. In the case of our patient, repeated blood cultures were negative, and Baehr, Klemperer and Schiff¹ reported 36 negative cultures with specimens of blood taken from 20 patients with the disease during febrile periods. Similarly, Libman and Sacks reported negative blood cultures in their cases.

The role of such photosensitizing agents as the porphyrins, a possible etiologic factor, suggested by the frequent history of abnormal sensitivity to sunlight and similar sources of radiation, is also obscure. Hematoporphyrins have been found to be present by some investigators and absent by others. In a recently reported series of 18 cases of acute and subacute disseminated lupus erythematosus, of which 9 were known to have ended fatally, Ludy and Corson²⁸ found hematoporphyrinuria in 4 of the fatal cases and in 3 others, in 3 cases it was not looked for, and in the other 8 it was not found. The authors also pointed out, in connection with a suggestion that lead may play a role in the etiology of the disease, that lead poisoning is a condition in which hematoporphyrinuria may be present. They were able to demonstrate pronounced spectroscopic evidence of lead in the skin in 15 of their cases, and a trace in the other 3, while in a series of 20 controls, lead was not found in 17 and there was only a trace in 3.

As Denzer and Blumenthal have pointed out,⁹ either clinical or pathologic evidence has demonstrated disseminated lupus erythematosus with a host of other conditions, such as tuberculosis, streptococcic infections, disease of the sinuses, carcinoma of the stomach, infections of the respiratory tract, pyonephrosis, dermatomyositis, scleroderma and periarteritis nodosa. It would seem, at least debatable, to conclude that such diverse associated conditions are necessarily related to the disease. On the other hand, in the continued absence of any recognizable specific etiologic factors it is reasonable to suppose that some peculiarity in the constitutional makeup of the patients with the disease might have brought about similar characteristic reactions to a variety of noxious agents. However, whether disseminated lupus erythematosus is, as

²⁸ Ludy, J. B., and Corson, E. F. Lupus Erythematosus. Increased Incidence, Hematoporphyrinuria and Spectroscopic Findings, *Arch. Dermat. & Syph.* **37**: 403 (March) 1938.

MacLeod²⁹ has written, "a cutaneous symptom of a peculiar type which may be called forth by a variety of causes, toxic or septic" and, as expressed by Baehi, Klempeier and Schiffin, "conditioned by a peculiarity in the constitutional reaction of the host," or whether, as might be suggested by the consistent clinical and pathologic picture, a uniform etiologic agent, such as a filterable virus, is responsible, cannot now be answered.

We can conclude, much as have Denzer and Blumenthal only that in this disease there is evoked a toxic agent which may produce widespread damage in the body, and which has a predilection for mesenchymal tissues, particularly those of endothelial and mesothelial structure.

SUMMARY

A case is presented of disseminated lupus erythematosus of the acute type in a male.

The disease occurs chiefly, though not exclusively, in females in the second to the fourth decade of life. Clinically, it often sets in with a distinctive type of erythematous cutaneous eruption, sometimes there is a history of unusual photosensitivity or preceding sunburn. The eruption, however, may not appear until some time after the onset of systemic symptoms, and undoubtedly cases may occur without the cutaneous manifestations. Another frequent initial clinical manifestation is polyarthralgia, which may be sufficiently severe to constitute an orthopedic problem.

The course of the disease is variable, being sometimes precipitous (*àgu d'emblée* type of Peinet) and sometimes drawn out, with remissions. Fever is usually present, often associated with pronounced prostration or asthenia and usually with clinical evidence of damage to serous membranes (arthralgias, pleuritis, pericarditis, ascites), depression of function of the bone-marrow (leukopenia, anemia, thrombopenia) and various hemorrhagic phenomena (purpura, petechiae, bleeding). There is usually evidence of renal damage, which may be severe. Evidence of endocarditis is less often clinically demonstrable. Enlargement of lymph nodes and, less often, of the spleen may be observed. Abdominal pain may be the basis for an erroneous diagnosis of an operable abdominal lesion.

Pathologically, there may be widespread distinctive vascular lesions, particularly of the renal glomeruli, which may show the characteristic "wire-loop" lesion described by Baehi, Klempeier and Schiffin. Non-bacterial pericarditis is common. There may be endocarditis of the type described by Libman and Sacks and by Gross, or there may be a

²⁹ MacLeod, J. M. H. Lupus Erythematosus, Arch. Dermat. & Syph. 9:1 (Jan.) 1924.

terminal nonbacterial thrombotic endocarditis. The disease may occur without endocardial changes or without a cutaneous eruption, and probably both of these, or indeed any of the features mentioned, may be absent. Notable when present is the occurrence of peculiar lesions in the lymph nodes and spleen. Microscopically, in the former there are distinctive areas of focal necrobiosis with or without peculiar hematoxylin-staining bodies, in the latter there are periaarterial areas of necrosis of the follicular lymphoid tissue, periaarterial fibrosis and intimal arterial thickening.

The causation of disseminated lupus erythematosus is not known. In any case, the disease does not seem to be of specific tuberculous or streptococcic origin. Serologic reactions may be positive for syphilis in the course of the disease, but they should be considered nonspecific. The nature of the pathologic changes suggests that they are the effects of a circulating toxic agent which has an affinity for mesenchymal tissues, particularly for endothelial and mesothelial structures. What role may be played in the elaboration of such a toxin by a specific etiologic agent or by a variety of causes in a constitutionally predisposed person is a question that must be left for future study.

PRIMARY SARCOMA OF THE PERICARDIUM

REPORT OF A CASE

ROBERT L PARKER, M D

ARCHIE H BAGGENSTOSS, M D

AND

THOMAS J DRY, M B

ROCHESTER, MINN

The heart is but rarely the site of a primary neoplasm, and it seldom becomes involved by metastatic malignant tumors. It is therefore of unusual interest to both clinicians and pathologists when a tumor involving this structure is discovered. Lymburner,¹ in a review of 8,550 necropsies, found 4 cases of primary tumor of the heart and 52 cases of secondary metastatic lesions of the heart. In a review of the literature,² he found reports of 226 instances of primary cardiac tumors. In a review of the subject in 1931, Yater³ found records of 46 instances of primary sarcoma of the heart. Additional cases have been reported by Morris,⁴ Barnes and his associates,⁵ Boman⁶ and Willius⁷ and from the Massachusetts General Hospital.⁸ Only 11 of these were cases of primary sarcoma of the pericardium.

From the Mayo Clinic. Dr. Parker is associated with the Division of Medicine, Dr. Baggenstoss with the Section on Pathological Anatomy and Dr. Dry with the Section on Cardiology.

1 Lymburner, R. M. Tumors of the Heart. Histopathological and Clinical Study of Four Primary and Fifty-Two Secondary Tumors of the Heart, Thesis, University of Minnesota, Mayo Foundation, March 1933.

2 Lymburner, R. M. Tumours of the Heart. Histopathological and Clinical Study, *Canad. M. A. J.* **30**:368-373 (April) 1934.

3 Yater, W. M. Tumors of the Heart and Pericardium. Pathology, Symptomatology and Report of Nine Cases, *Arch. Int. Med.* **48**:627-666 (Oct) 1931.

4 Morris, J. J. Primary Sarcoma of Heart, *J. Lab. & Clin. Med.* **18**:935-940 (June) 1933.

5 Barnes, A. R., Beaver, D. C., and Snell, A. M. Primary Sarcoma of the Heart. Report of a Case with Electrocardiographic and Pathological Studies, *Am. Heart J.* **9**:480-491 (April) 1934.

6 Boman, P. G. Primary Sarcoma of the Pericardium. Report of a Case, *Ann. Int. Med.* **12**:258-266 (Aug) 1938.

7 Willius, F. A. Cardiac Clinics. XLIX. Clinic on Refractory Congestive Heart Failure of Relatively Short Duration, Comments, Postmortem Findings (Primary Fibrosarcoma of the Right Auricle), *Proc. Staff Meet., Mayo Clin.* **13**:331-335 (May 25) 1938.

8 Primary Sarcoma (Probably Fibrosarcoma) of the Right Auricle, Cabot Case 22491, *New England J. Med.* **215**:1082-1085 (Dec 3) 1936.

The majority of primary tumors of the heart are benign. About 25 per cent are malignant. The most common malignant tumors are sarcomas. They may be classified as spindle cell, round cell or mixed cell sarcomas and most frequently arise from the auricles. The cardiac valves, the ventricles and the pericardium are less common sites of origin. Among other types of primary tumors of the heart are myxomas, rhabdomyomas, rhabdomyosarcomas, fibromas, lipomas, angiomas, hemangio-endotheliomas and lymphangio-endotheliomas.

The diagnosis of a primary tumor of the heart, because of the extreme rarity of such neoplasms and the lack of recognizable clinical criteria, is usually made by the pathologist. Yet, if the clinician would bear in mind the possibility of such a lesion whenever a clinical picture presents itself which is not explicable on the basis of one of the more common cardiac lesions, the diagnosis might be made during the life of the patient.

Symptoms and signs which are likely to arouse clinical suspicion of tumor of the heart are (1) progressive circulatory failure for which no obvious anatomic basis can be demonstrated, (2) signs pointing to valvular defects with murmurs, the character of which may change from day to day or may be unduly influenced by change in posture, (3) signs of mediastinal tumor associated with changes in the roentgenologic silhouette of the heart and (4) recurrent hemorrhagic pericardial effusion.

REPORT OF A CASE

History—A man aged 35 had enjoyed excellent health until January 1938 (nine months prior to his admission to the Mayo Clinic), when, for three days, he complained of substernal pain aggravated by respiration and associated with dyspnea on slight exertion. These symptoms subsided and did not return until three months later, when, for seven days, similar thoracic pain and dyspnea were noted. In June the patient complained of a recurrence of this distress, associated on this occasion with fever. Examination by his physician disclosed advanced enlargement of the cardiac silhouette. After three weeks' rest in bed his condition improved and he was able to return to light work. His strength, however, never returned to normal, and dyspnea prevented his undertaking any strenuous activity.

A few weeks later he experienced sharp pain in the right portion of the thorax, augmented by inspiration and associated with cough and slight hemoptysis. The pleuritic pain subsided spontaneously. He continued, however, to have a non-productive cough, which was aggravated by lying down, and he noted that when he assumed a recumbent position his face became red and his features distorted by swelling. This was relieved by sitting up. At night attacks of coughing occurred, and on numerous occasions the spasm of coughing precipitated sudden loss of consciousness associated with deep cyanosis of the face. To prevent these attacks, he found it necessary to sleep in an upright position.

Physical Examination—On September 8 the patient appeared well developed and well nourished. His blood pressure was 122 systolic and 80 diastolic. Attention was immediately aroused by the objective signs of venous obstruction. The patient's cervical veins were distended, and when he lay down his face and neck became cyanotic. The heart was greatly enlarged. The area of cardiac dullness

extended to the anterior axillary line on the left and to the midclavicular line on the right. The cardiac tones were clear, and there were no murmurs. Except for rales at the base of the left lung and diminished breath sounds over the lower lobe of the right lung, no significant pulmonary signs were noted. There was a marked delay in the emptying of the veins on elevation of the arm. A teleroentgenogram of the thorax disclosed a huge enlargement of the cardiac silhouette (fig 1). The heart measured 11 cm to the right and 15 cm to the left of the midsternal line, and the diameter of the thorax was 34 cm. In the right lung there was interlobar pleural thickening, and at the level of the fifth rib there was a region of localized infiltration. The roentgenologist, who carried out a fluoroscopic examination of the heart, noted a diminution in the amplitude of

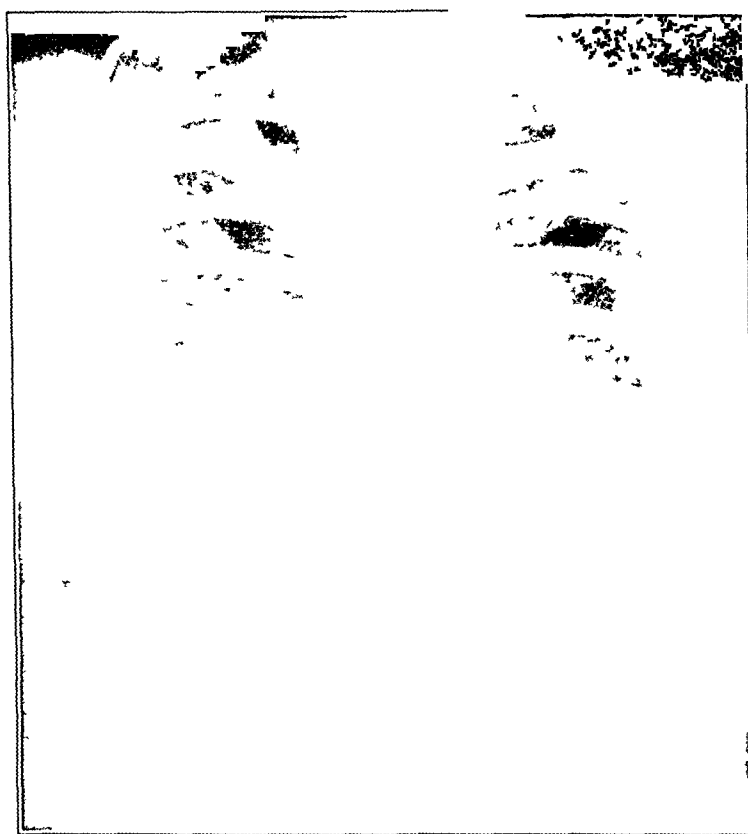


Fig 1—Teleroentgenogram of the thorax, showing the massive enlargement of the cardiac silhouette

contraction in all chambers and suggested the existence of pericardial effusion. The electrocardiogram showed a sinus rhythm, slurred QRS complexes in derivations I, II and III, right axis deviation and inverted T waves in derivations II and III. The T wave was positive in the standard fourth lead. The results of routine examinations of the urine and blood, including serologic examinations, were negative.

In brief, the clinical picture was that of cardiac decompensation which had developed relatively rapidly in a comparatively young man who had experienced several episodes of retrosternal thoracic pain aggravated by respiration. On one occasion he experienced pain of pleuritic character in the right portion of the thorax associated with hemoptysis. Objectively, the striking signs were obvious and unduly marked venous engorgement, marked cardiac enlargement, with fluoroscopic evidence of diminution in the amplitude of cardiac contraction, and an electrocardiographic pattern signifying predominant strain of the right ventricle.

Course—The patient was hospitalized for further study, and an attempt was made to alleviate congestive failure. After administration of digitalis and intravenous administration of mercurial diuretics, moderate diuresis was provoked and temporary improvement resulted. The venous pressure, however, remained high (300 mm of water), an observation which we were led to believe indicated mechanical obstruction to the return circulation rather than an elevation caused by congestive failure alone. Paracentesis of the pericardium was performed, but it did not reveal fluid in the pericardial sac. Further efforts to control cardiac failure met with no success. He became more cyanotic, in spite of the administration of oxygen, and died seventeen days after admission to the hospital.

Speculation as to the causative background of this striking clinical picture included consideration of all possible causes of cardiac enlargement in a person whose history prior to the onset of his symptoms nine months before we saw him was singularly negative.

Valvular and congenital cardiac disease in the absence of bruits, previous hypertension in the face of a negative history, lack of retinal changes and an electrocardiographic pattern indicating strain of the right ventricle all precluded serious consideration. Nor would the cardiac hypertrophy occasionally seen after myocardial infarction fit the picture despite a history of thoracic pain and hemoptysis (which might otherwise have been explained on the basis of pulmonary embolism secondary to dislodgment of a mural thrombus from the interventricular septum).

Still less would the pathologic entities already mentioned explain the most striking phenomenon presented, namely, the unduly high venous pressure, which was out of all proportion to the other evidences of congestive failure. This pressure had the characteristics of mechanical obstruction to the venous return rather than of venous engorgement incidental to myocardial failure, and, in view of the fluoroscopic observation of limitation in the excursions of cardiac contractions, the picture of constricting pericarditis was strongly suggested. While the possibility that this constricting factor might actually be a primary malignant process had been casually mentioned in discussion, it was not seriously considered in the clinical evaluation of this case. Perhaps one of the main reasons for failing to arrive at the correct pathologic diagnosis—indeed a reason that actually was misleading—was the electrocardiographic pattern. Thus, the evidence in favor of hypertension within the pulmonary circuit was seriously considered because of the electrocardiographic observations, in conjunction with the extreme cyanosis and the marked venous congestion. A case reported by Barnes and Yater,⁹ in which multiple thrombi in the pulmonary arteries gave

9 Barnes, A. R., and Yater, W. M. Paroxysmal Tachycardia and Alternating Incomplete Right and Left Bundle-Branch Block with Fibrosis of the Myocardium. Failure of the Right Ventricle Due to an Ancient Thrombus in the Pulmonary Arteries, Fibromyxoma of the Left Auricle Occluding the Mitral Orifice, and Simulating Mitral Stenosis, *M. Clin. North America* **12** 1603-1615 (May) 1929.

rise to congestive heart failure, with cardiac hypertrophy and clinical and electrocardiographic evidence of strain on the right ventricle, illustrates this syndrome.

The other known causes of pulmonary hypertension did not seem adequate to explain our findings. Appreciable emphysema was not evident, certainly not enough to produce severe pulmonary hypertension. In cases of advanced primary pulmonary arteriolar sclerosis with failure of the right ventricle, a prolonged history of progressive dyspnea prior to the onset of congestive failure is usually noted. Even assuming the possibility of thrombosis, *in situ*, of a branch of the pulmonary artery, which was suggested by points already mentioned, we could not expect hypertension in the lesser circulation alone to produce the extreme cardiac hypertrophy noted in this instance.

Similarly, pericarditis with massive effusion would explain the dramatic enlargement of the cardiac silhouette associated with signs of circulatory obstruction. This condition, however, was excluded by the performance of paracentesis of the pericardium. Our failure to find fluid in the pericardial sac in this instance did not exclude the possibility of pericardial disease. In cases of constrictive pericarditis associated with calcification of the pericardium, the heart is seldom found to exhibit marked hypertrophy. However, in the presence of chronic adhesive pericarditis, with or without rheumatic valvular deformities, the heart may be markedly enlarged. It has already been mentioned that examination of our patient did not disclose physical findings indicative of valvular deformity. It is, of course, not unusual to find modification of the classic auscultatory signs of valvular deformities when congestive cardiac failure is present. Occasionally, the physician may be amazed to observe at autopsy advanced valvular disease, of which, because of the disturbed cardiac dynamics associated with congestive cardiac failure, the usual signs were either absent or so minimal during the patient's life as to be considered insignificant. In estimating the condition of this particular patient, however, it seemed to us that the recent onset and rapid progression of cardiac disability in the absence of positive auscultatory signs were not in accord with a diagnosis of valvular disease.

We attempted to evaluate these possible causative factors in the light of the essential observations made during examination of this patient. It was our impression that the most logical explanation of the cardiac hypertrophy associated with venous circulatory obstruction was constrictive mediastinopericarditis.

Necropsy—The body weighed about 180 pounds (81.6 Kg). There was about 100 cc of clear yellow fluid in the peritoneal cavity. When the pleural cavities were opened, a large mass was seen to fill the middle portion of the mediastinum.

and a large part of the left side of the thorax. The mass appeared to be enclosed within a distended pericardial sac, which measured 21 cm transversely. This mass compressed the left lung, especially the lower lobe, which was collapsed. The right pleural cavity contained 1,200 cc and the left 200 cc of clear brown fluid. The mass within the pericardial sac was firm and solid except for a portion near the base of the heart, which was fluctuant. Attempts to open the pericardial sac in the usual manner were unsuccessful, because the parietal pericardium was firmly adherent to the underlying tissue. When the fluctuant portion was opened, a large amount of thick, reddish gray gelatinoid material escaped.

The entire mediastinal mass was dissected and removed from the body. During this procedure, the left jugular and both innominate veins were seen to contain mural thrombi which extended down into the superior vena cava and almost completely blocked the lumens of these veins. The entire mass weighed 3,000 Gm. It presented an irregularly ovoid shape and measured 23.5 by 21 by 9.5 cm (fig 2). Superiorly, it extended 2 cm above the bifurcation of the trachea, but nevertheless



Fig 2—Cross section of the mass of the tumor, showing the heart encased by the neoplasm. Note the neoplastic invasion of the left ventricle.

seemed to be enclosed by a fibrous capsule, which was presumably the pericardium. Laterally, it had grown into the hilar regions of both lungs, without, however, metastasizing to the lymph nodes. Inferiorly, it was attached to the diaphragm. Posteriorly, it surrounded and compressed the pulmonary blood vessels.

On cross section it was seen that a yellowish white tumor mass completely encircled the heart and filled and distended the pericardial sac. In some regions, this tumor tissue was firm, while in other regions it was soft and encephaloid. Large and small areas of hemorrhage were situated throughout the tumor. Some of them apparently had been present for some time, as evidenced by their yellow, brown and orange discoloration. Firm white bands of fibrous connective tissue extended through the tumor.

Serial cross sections revealed the fact that the tumor reached its greatest size in the region lateral to the left ventricle, where it measured 12 cm in thickness. Around the base of the heart and in the region of the right ventricle, the encircling sheath of tumorous tissue varied from 1 to 5 cm in thickness. The tumor as a

whole was rather sharply demarcated from the heart muscle but in some portions appeared to invade it. The tumor appeared to be entirely enclosed within the pericardial sac, except in both hilar regions of the lungs, where it had broken through. The hilar lymph nodes were not, however, invaded by the tumor. Superiorly, the tumor surrounded the great blood vessels and compressed them somewhat.

The heart muscle was reddish brown and exhibited no gross lesions. The valves and the endocardium appeared normal.

The remaining organs disclosed nothing of note except slight evidence of chronic passive congestion in the lungs and liver.

The diagnoses from an anatomic point of view were sarcoma of the pericardium with invasion of the heart, thrombosis of the left jugular and innominate

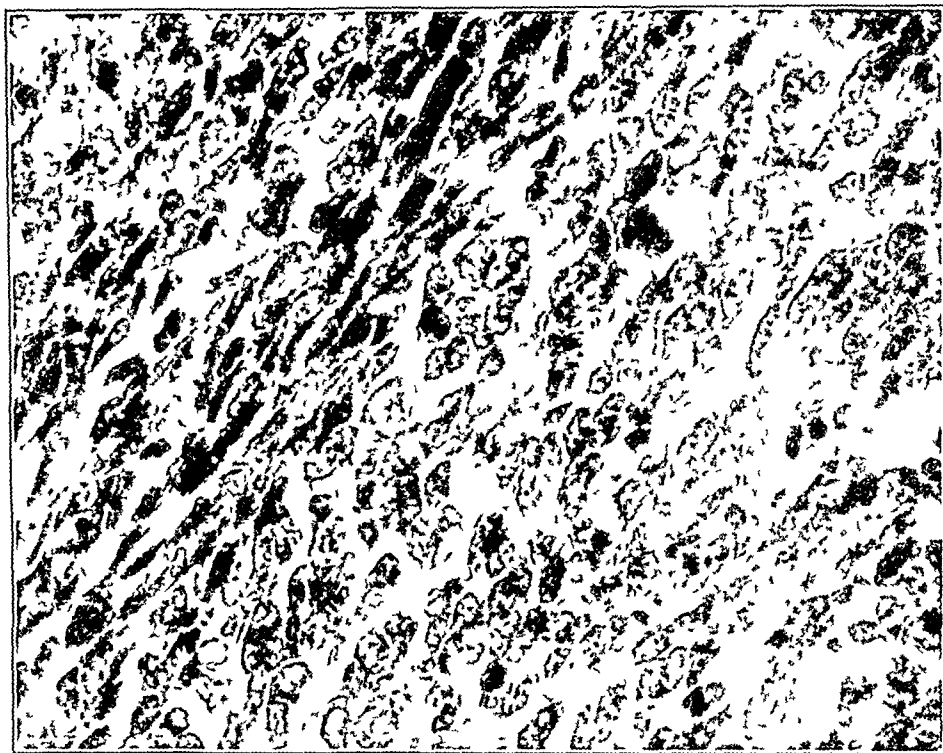


Fig 3—A section through the sarcomatous portion of the pericardium, showing the parallel arrangement of the spindle-shaped and oval cells ($\times 500$)

veins and the superior vena cava, hydrothorax, with 1,200 cc of fluid on the right and 200 cc on the left, ascites, with 100 cc of fluid, atelectasis of the lungs, and chronic passive congestion of the lungs and liver.

Microscopic Examination—The structure of the tumor was uniform. It consisted of large spindle-shaped and oval cells arranged for the most part in parallel rows (fig 3). The cells had a narrow zone of pink-staining cytoplasm, which tapered at the ends and occasionally extended out into long fibrils. In many regions the cells were closely packed, and distinct cell boundaries were difficult to delineate. The nuclei were large, spindle-shaped or ovoid, and pale staining. The chromatin was arranged in a network with occasional condensations, especially at the nuclear membrane. Nucleoli were infrequent. Mitotic figures were numerous.

Sections impregnated with silver by the Bielschowsky technic revealed many fine fibrils in close association with the tumor cells. These reticular fibrils were hypertrophied at the borders of the cardiac muscle and in the regions where they became continuous with the connective tissue septums of the tumor. The fibers of the reticulum were larger and more numerous between the fibers of the cardiac muscle than they were in the tumor.

Evidences of degenerative cellular changes, such as pyknosis and karyorrhexis, were diffusely scattered throughout the tumor, and in some portions distinct foci of necrosis were seen. Hemorrhages were numerous.

Sections which included both the tumor and the cardiac muscle disclosed invasion of the myocardium (fig 4). In some regions, the muscle cells were completely surrounded by neoplastic cells. There was destruction of the muscle cells with proliferation of fibrous connective tissue.

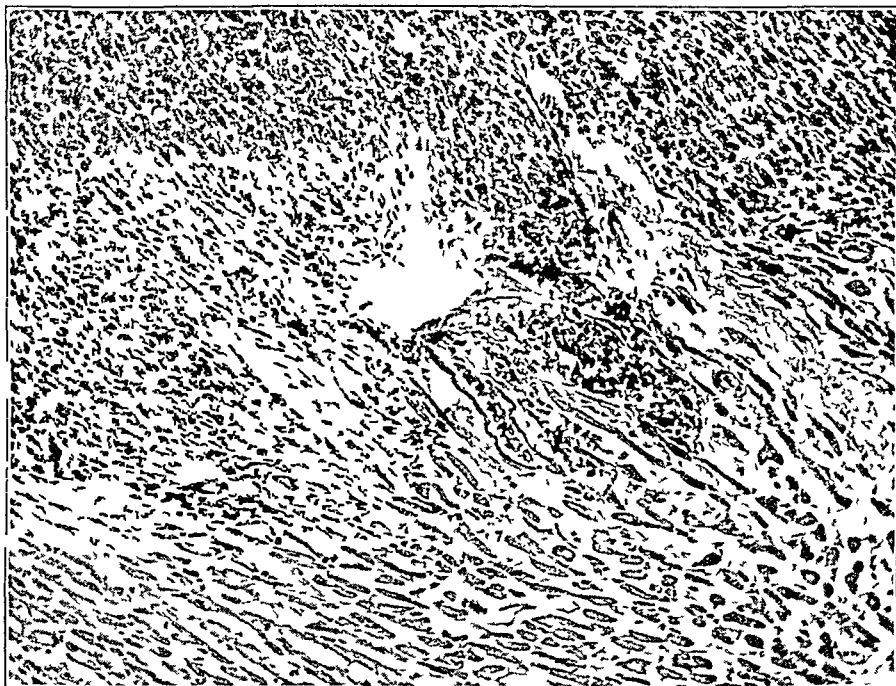


Fig 4—A section through the myocardium, showing invasion of that muscle by sarcomatous spindle-shaped cells.

COMMENT

In the light of the necropsy, the clinical picture is easily understood.

The thoracic pain may be explained by the malignant process in the pericardium. The apparent progressive massive cardiac enlargement, together with the roentgenoscopic finding of diminished amplitude of cardiac contraction, likewise is explained by the tremendous tumor in which the heart was encased. The venous obstruction was, as we had thought, the result of mechanical obstruction of the large veins which enter the heart. There was not sufficient displacement in the anatomic axis of the heart to account for the finding of right axis

deviation in the electrocardiogram. Yet this sign, together with the negativity of the T wave in leads II and III, may be accounted for by the manner in which the mass of the tumor had surrounded and compressed the great blood vessels at the base of the heart, especially the pulmonary vessels, throwing a strain predominantly on the right ventricle.

We believe that the episodes of loss of consciousness were the result of cerebral anoxemia secondary to venous stasis. Other instances are on record¹⁰ in which attacks of unconsciousness were associated with extreme cyanosis. Their relation to posture is explained by the increased or decreased venous drainage dependent on gravity. Thus, all the features of this case which had proved to be so perplexing from the standpoint of clinical diagnosis became explainable in the light of the pathologic observations. We feel that had we not been unduly influenced by the extreme rarity of primary cardiac neoplasms and had we discounted certain confusing features in the electrocardiographic pattern, the correct diagnosis might have been made during the life of the patient.

10 Montgomery, G. L. A Case of Pulmonary Artery Thrombosis with Ayerza's Syndrome, *J Path & Bact* **41** 221-230 (Sept) 1935.

EVALUATION OF THERAPY IN MYASTHENIA GRAVIS

NATHAN S SCHLEZINGER, M D, M Sc D

PHILADELPHIA

The disease entity known as myasthenia gravis was first described by Willis¹ in the seventeenth century. Although this condition is relatively easy to recognize clinically, its cause has remained obscure. Pathologically in many cases there are variable degrees of nonspecific degenerative muscle atrophy. In more than 50 per cent of cases focal collections of small round cells have been observed in muscles and other organs. These small foci of cells have been termed "lymphorrhages" and when present are diagnostically significant. A relatively large number of cases have been reported in which thymic neoplasms existed. The conspicuous symptomatic features of myasthenia gravis are excessively rapid fatigability of muscles in action and quick restitution of function on relaxation. The muscular exhaustibility may be elicited in the form of a characteristic electrical reaction which has been termed the Jolly reaction.

In this article no effort will be made to discuss in detail the etiology, pathology, semiology and diagnosis of myasthenia gravis. For such a discussion the reader is referred to the excellent review of the subject published by Keschner and Strauss². The present study is primarily concerned with the question of treatment of this disease. Therapy has been largely ineffective until recently, in recent years, however, there have been increasingly numerous reports describing beneficial effects following the administration of a wide variety of drugs, including amino-acetic acid, ephedrine, extract of the anterior lobe of the pituitary gland, physostigmine, prostigmine and potassium chloride. Some reports with regard to a few of these remedies have contradicted the favorable reports made by others using the same drug. In interpreting such contradictory reports one must remember that falsely beneficial results may have been obtained because of the spontaneous remissions which are apt to occur.

From the Neurologic Division of the Montefiore Hospital for Chronic Disease, New York

1 Willis, cited by Guthrie, G. L. "Myasthenia Gravis" in the Seventeenth Century, *Lancet* 1:330 (Jan. 31) 1903

2 Keschner, M., and Strauss, I. Myasthenia Gravis, *Arch. Neurol. & Psychiat.* 17:337 (March) 1927

in this condition. One must also consider the fact that considerable difficulty may be encountered in differentiating clinically between myasthenia gravis and the myasthenic syndrome due to encephalitis or to other specific etiologic factors.

In determining the effect of therapy, some observers have utilized the response to various functional tests for motor power and fatigue. Others have emphasized subjective alterations in the patient as a means of judging the effectiveness of treatment. It would seem that in order to evaluate properly the results of therapy it is necessary to have some objective index of the patient's muscular strength. This index should be capable of standardization as far as possible and should thus be valid for comparison in the individual patient. With this view in mind, certain test procedures have been selected for the measurement of muscle power and fatigue. This study consists of the utilization of such tests in order to evaluate the relative effectiveness of certain forms of therapy that have been proposed. A group of 7 cases in which the diagnosis of myasthenia gravis was clearly established has been used in this investigation. The results in each case have been tabulated (tables 1 to 7).

The remedies which were administered to the various patients consisted of aminoacetic acid, ephedrine, a combination of aminoacetic acid and ephedrine, anterior pituitary extract,³ prostigmine and a combination of prostigmine and ephedrine. These drugs were given successively for periods approximating one month each. Whenever possible, an initial period of one month without medication was used as a control for each patient. For various reasons (noted in the description of each case) it was not possible to give all of the aforementioned remedies in each case. The period of medication with anterior pituitary extract approximated ten days instead of one month. In instances in which prostigmine was administered parenterally, examination was made one hour after the injection. For all other forms of therapy examination was made at 9 a. m., the patient remaining in bed until this hour.

The dosage of various medications administered during the course of this study was as follows: aminoacetic acid, 10 Gm. three times a day, ephedrine, 0.03 Gm. three times a day, anterior pituitary extract, 1 cc. by hypodermic injection twice a day, prostigmine methylsulfate (1:2,000), 3 cc. by hypodermic injection, and prostigmine bromide, 90 to 165 mg. daily by mouth (given three or four times a day).

TEST PROCEDURES

A preliminary trial period during which a wide variety of test procedures were used for patients with myasthenia gravis and for controls served to eliminate

³ The form of extract of the anterior lobe of the pituitary gland used in this study was antuitrin.

a number of tests that were found to be unsatisfactory. In the more reliable test procedures the factor of dependence on the patient's cooperation, although still present to some extent, was minimized. Standardization of other variable factors was attempted whenever possible. Patients were always examined at the same time of day. Excessive clothing was removed, and draping of the body was designed to allow complete freedom of motion of all extremities. Test procedures were performed in the same sequence at each examination. Each test was done twice at every examination, and the maximum result was always taken as the one for comparison. All dynamic tests were timed so that the speed of performance could thereby be standardized. During an examination the patient was seated in a chair the seat level of which was 47 cm from the floor.

In choosing satisfactory test procedures, the greatest difficulty was encountered with the muscles innervated by the cranial nerves. Quantitative measurements of blinking, squinting and biting were attempted but proved to be unreliable because of the excessive variability of reaction. Protrusion of the tongue was found to be the only satisfactory method of testing the strength of the bulbar muscles. This procedure has been termed the dynamic lingual test and consists of repetitive, forcible protrusions of the tongue at a definite rate of speed continuing until weakness prevents protrusion beyond the margins of the lips.

Less difficulty was encountered in choosing reliable tests of motor power in the extremities. The static arm test consisted of continuous abduction of the extended arm while supporting a hand weight of 1,000 Gm above a level of 84 cm from the floor, the test was terminated on inability to maintain this level. Similarly, the static leg test consisted of continuous elevation of the extended leg above a level of 43 cm from the floor, the test was terminated by inability to maintain this level.

The dynamic arm test consisted of repetitive elevation of the extended arm from the knee to a vertical position at a definite rate of speed, the test was terminated by failure to elevate the arm completely. The dynamic leg test consisted of alternate extension-flexion movements at the knee at a definite rate of speed, the test was terminated by inability to continue this procedure. Similarly, the dynamic forearm and toe tests, which were used in 1 case, consisted of alternate extension-flexion movements at a definite rate of speed, continued to exhaustion. In a number of cases the power of the hand grasp was determined by means of a dynamometer. The average of four alternately successive attempts was used as the basis for comparison. The dynamometer has been used also to determine the duration of effect resulting from the hypodermic administration of prostigmine.

REPORT OF CASES

CASE 1—H. A., a man aged 51 years, a carpenter, was admitted to the Montefiore Hospital on Oct 29, 1934. He had had typhus fever at 15 years of age and frequent colds since early childhood. At various times he had had operations, including bilateral herniorrhaphy, removal of a testicle and appendectomy. In 1914 he had sharp pains in both shoulders, which persisted until 1922 and subsequently recurred infrequently. In 1934 he had general malaise without any specific complaints. In April there was sudden onset of pain in the right side of the chest, radiating to the right shoulder and arm and associated with slight fever. One month later a dull pain in the back of the neck appeared and was accompanied by a sensation of heaviness, with difficulty in lifting the head, difficulty in mastication and dysphagia soon appeared. The speech became nasal. Weakness of the left arm developed and was soon followed by weakness of the right arm. All of

these symptoms became worse, and in addition there were dropping of the lower jaw, drooling of saliva, ptosis on the left and episodes of dyspnea

The significant physical findings on the patient's admission to the hospital were weakness of the body musculature generally with rapid fatigability, weakness of the facial muscles with inability to close the eyes, weakness of the muscles of mastication and of the tongue, and nasal speech

Laboratory Data—Urinalysis and a blood count gave results within normal limits. The value for blood sugar was 100 mg, that for urea nitrogen 13.8 mg, that for calcium 11.5 mg and that for phosphorus 4.6 mg, per hundred cubic centimeters. Serologic examination of the blood and of the spinal fluid did not reveal syphilis. A myasthenic electrical reaction was obtained in the muscles of the left upper extremity.

Course—Previous to the period of experimental therapy the patient received combined aminoacetic acid and ephedrine medication, with resultant improvement. When all medication was withdrawn the patient complained bitterly of increasing

TABLE 1—Results of Therapy in Case 1

		Medicament			
		None	Aminoacetic Acid	Ephedrine	Aminoacetic Acid Plus Ephedrine
Tongue		60 1 05	55 1 00	63 1 05	77 1 20
Arms (static)	Right	23	20	1 40	1 48
	Left	17	20	1 20	1 42
Arms (dynamic)	Right	25 33	23 33	59 1 20	80 1 40
	Left	19 25	19 27	36 45	67 1 27
Legs (static)	Right	36	35	52	56
	Left	45	42	37	58
Legs (dynamic)	Right	47 1 08	32 40	58 1 14	58 1 17
	Left	40 1 03	31 45	39 53	58 1 16

* In tables 1 to 7, inclusive the numbers represent the period (in minutes and seconds) during which the patient was able to maintain the muscular effort required by the test

weakness, dysphagia and dyspnea. During the period of aminoacetic acid therapy weakness persisted and there was a loss of 9 pounds (4.1 Kg.) in weight. During the period of ephedrine therapy there was a definite increase in strength, noted chiefly in the extremities. During the period of combined aminoacetic acid and ephedrine therapy this improvement persisted and was accompanied by improved speech and subsidence of dysphagia. Subsequently the patient was given prostigmine by injection but had an unfavorable reaction. He complained of marked nausea and colicky abdominal pain starting one-half hour after the injection and lasting two hours. Further use of prostigmine was refused by the patient. He was discharged on Dec. 8, 1935.

Comment—The objective results of therapy in this case are shown in table 1. The beneficial effect of ephedrine therapy was conclusively demonstrated. Aminoacetic acid therapy alone was apparently ineffective. The slightly greater benefit obtained with combined medication as compared with ephedrine medication may possibly be due to the more prolonged use of the latter.

CASE 2—A M, a man aged 63 years, was admitted to the Montefiore Hospital on Aug 8, 1935, with a history of nuchal pain beginning in May 1934 and soon followed by weakness in closing the jaws. The pain subsided, but drooping of the left eyelid appeared. In August diplopia was noted and was gradually followed by dysphagia, nasal regurgitation and thick speech. All of these symptoms became more marked. In May 1935 there was an episode characterized by the sudden onset of abdominal pain and dyspnea, this was diagnosed as a "heart attack." Subsequently the nuchal pain recurred.

The noteworthy physical findings on admission were an enlarged heart with generalized arteriosclerosis, chronic bronchitis with pulmonary emphysema, generalized motor weakness with rapid fatigability, myasthenic facies, bilateral paresis of the muscles of mastication and those of the tongue and palate, nasal dysarthric speech, dysphagia, and diplopia.

Laboratory Data—Urinalysis and blood count gave results within normal limits. The value for blood sugar was 105 mg, that for urea nitrogen 17.1 mg, that for calcium 10.9 mg and that for phosphorus 4.4 mg per hundred cubic centimeters.

TABLE 2—Results of Therapy in Case 2

		Medicament					
		None		Aminoacetic Acid		Ephedrine	
Tongue		32	29	34	32	53	42
Arms (static)	Right	30		46		1	13
	Left	22		33			54
Arms (dynamic)	Right	34	43	39	55	61	1 22
	Left	31	38	33	43	42	57
Legs (static)	Right		21		23		37
	Left		25		30		32
Legs (dynamic)	Right	30	35	26	31	38	48
	Left	25	29	27	33	41	49

Serologic tests of the blood and spinal fluid showed no evidence of syphilis. The basal metabolic rate was —4 per cent. The electrocardiogram showed right axis deviation. A myasthenic electrical reaction was obtained in the facial and sternomastoid muscles. Biopsy of muscle tissue showed nonspecific degeneration.

Course—During the period of no medication following admission to the hospital the patient displayed increasing weakness associated with paroxysmal dyspnea. During the period of aminoacetic acid medication the extremities were slightly stronger, but there was no improvement in the bulbar symptoms. During the period of ephedrine medication there was a definite increase in muscular strength generally and a diminution in the intensity of the bulbar symptoms. This improvement persisted during the short period of combined ephedrine and aminoacetic acid medication until Jan 5, 1936, when there was a sudden exacerbation of symptoms associated with the development of pulmonary edema. Death due to coronary thrombosis occurred on January 9. In the terminal stage the bulbar symptoms could be temporarily and partially relieved by the administration of prostigmine hypodermically.

Comment—The objective results of therapy in this case are shown in table 2. The ineffectiveness of aminoacetic acid and the effectiveness of ephedrine are conclusively demonstrated.

CASE 3—I K, a man aged 24, a furrier, was admitted to the Montefiore Hospital on Sept 18, 1931. In December 1929 he noticed that his lower extremities were gradually becoming weaker. Soon afterward the lifting of light objects became difficult. Six months later there appeared generalized weakness and occasionally diplopia. During the next six months he began to stutter when fatigued, and chewing became difficult. As his condition progressed he noticed that he was generally more fatigued in the morning than in the evening.

The significant physical findings on admission were generalized muscle weakness with rapid fatigability, bilateral ptosis with mechanically demonstrable myasthenia, multiple extraocular muscle pareses, nasal speech, dysphagia, and difficulty in chewing.

Laboratory Data—Urinalysis showed no abnormality. The blood count was within normal limits. The value for blood sugar 82 mg, that for urea nitrogen 12.3 mg, that for calcium 10.1 mg and that for phosphorus 3.3 mg per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid did not reveal

TABLE 3—Results of Therapy in Case 3

		Medicament													
		None		Amino acetic Acid		Ephedrine		Amino acetic Acid Plus Ephedrine		Anterior Pituitary Extract (Hypo)		Prostig mine (8 Tab lets)		Prostig mine (8 Tab lets) Plus Ephedrine	
Tongue		45	40	44	37	36	29	40	34	25	19	81	1 01	82	56
Arms (static)	Right		50		57		1 58		1 54		1 04		2 16		2 36
	Left		40		46		1 26		1 30		1 04		1 48		2 23
Arms (dynamic)	Right	38	52	38	52	42	1 02	58	1 15	37	48	81	1 52	95	2 09
	Left	27	36	41	55	39	53	48	1 02	32	40	64	1 29	81	1 46
Legs (static)	Right		32		36		58		53		41		1 04		1 28
	Left		31		30		52		47		37		50		1 07
Legs (dynamic)	Right	27	32	34	40	40	43	45	50	23	30	71	1 15	92	1 28
	Left	26	28	35	38	41	44	48	56	34	33	65	1 09	104	1 37

syphilis. The basal metabolic rate was —19 per cent. The electrocardiogram showed sinus rhythm. A myasthenic electrical reaction was obtained in the left biceps and in the facial muscles.

Course—Prior to the period of experimental therapy the patient had been treated at various times with gelatin, ephedrine or aminoacetic acid. A combination of the last two forms of medication was beneficial. When all medication was withdrawn there were marked increase in muscular fatigability, increase in diplopia and recurrence of dysphagia. During the period of aminoacetic acid medication the aforementioned exacerbation of symptoms persisted. During the period of ephedrine medication, after two weeks the patient noticed a general increase in muscular strength, particularly in the extremities, and a subsidence of dysphagia. During the period of combined aminoacetic acid and ephedrine medication the symptomatic improvement persisted. During the period of medication with anterior pituitary extract there was an exacerbation of symptoms similar to that noted when no medication was given. In response to the administration of prostigmine hypodermically there was noted within fifteen minutes a deep tingling sensation in the face and then throughout the body, which was shortly followed by an increase in strength of the muscles, including those innervated by the cranial nerves.

(fig 1) The maximum increase in strength appeared at the end of one hour and was followed by a gradual subsidence. During the period of oral administration of prostigmine the patient noticed a definite increase in strength affecting the entire body musculature. A slight feeling of nausea was occasionally present after the administration of prostigmine. During the period of combined prostigmine and ephedrine medication the increased muscular strength seemed to last longer than it did after medication with prostigmine alone.

Comment—The objective results of therapy in this case are shown in table 3. The ineffectiveness of aminoacetic acid and of anterior pituitary extract is clearly shown. The beneficial effect of ephedrine is demonstrated in the extremities. The striking effectiveness of prostigmine was noted both in the tongue and in the extremities. Combined

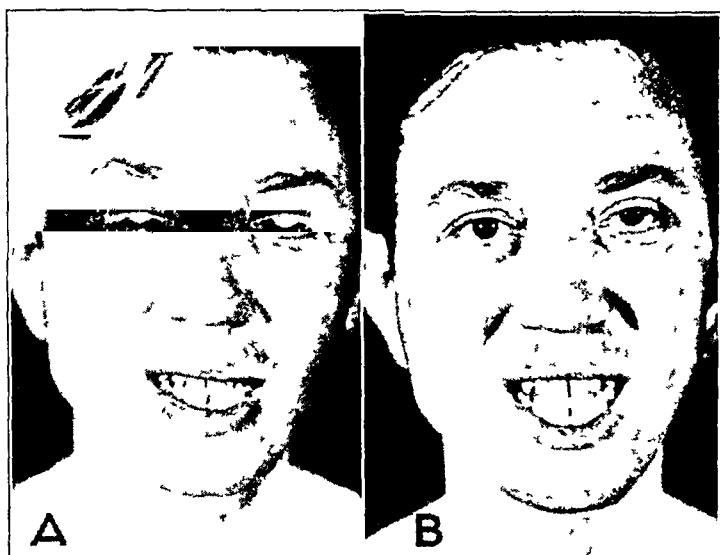


Fig 1 (case 3)—Facial appearance of the patient (A) without medication and (B) after hypodermic administration of prostigmine.

prostigmine and ephedrine medication appeared to be slightly more potent than prostigmine therapy alone.

CASE 4—J W, a woman aged 45, a housewife, was admitted to the Montefiore Hospital Nov 13, 1934, with a history of diplopia and fatigability in speaking, both starting one year previously. These symptoms were associated with gradually increasing weakness and dysphagia. There was a gradual loss of weight, amounting to 100 pounds (45.4 Kg) previous to admission.

The significant physical findings on admission were emaciation, generalized muscular wasting but no focal atrophies or fibrillations, generalized muscular weakness with rapid fatigability, generalized hyperreflexia, myasthenic facies, myasthenic weakness of all the musculature innervated by the cranial nerves including the eyes, face, tongue, jaws and palate, dysphagia, and nasal speech with the early appearance of aphonia.

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Laboratory Data—Urinalysis revealed no abnormality. The blood count showed hemoglobin, 74 per cent, red blood cells, 3,030,000 per cubic millimeter,

white blood cells, 4,700 with polymorphonuclears 79 per cent, lymphocytes 13 per cent and monocytes 8 per cent. Achlorhydria was present after administration of histamine. The value for blood sugar was 88 mg, that for urea nitrogen 9.3 mg, that for calcium 9.7 mg and that for phosphorus 5.1 mg per hundred cubic centimeters. Serologic tests of the blood and spinal fluid serology showed no evidence of syphilis. The basal metabolic rate was 0. The electrocardiogram showed sinus rhythm. A myasthenic electrical reaction was obtained in many of the involved muscles.

Course—Prior to the experimental period of therapy the patient received combined ephedrine and aminoacetic acid medication with resultant improvement in her condition. When all medication was withdrawn there was a marked increase in weakness together with increased dysphagia and dysarthria. During the period of aminoacetic acid medication the patient complained bitterly of increasing weakness, and she was confined to bed much of the time. During the period of ephedrine

TABLE 4—Results of Therapy in Case 4

		Medicament											
		None		Aminoacetic Acid		Ephedrine		Aminoacetic Acid* Plus Ephedrine		Anterior Pituitary Extract* (Hypo)		Prostigmine (Hypo)	
Tongue		50	42	53	48	42	35	48	45	32	33	144	2 07
Arms (static)	Right	1	04	1	07	1	08	1	11	40		1	44
	Left		45		51		1 06		1 16	33			1 30
Arms (dynamic)	Right	28	42	33	48	39	49	41	57	21	31	45	58
	Left	23	34	29	42	35	48	36	51	18	25	32	38
Legs (static)	Right	23		24		26		24		23		26	
	Left	30		36		36		38		31		40	
Legs (dynamic)	Right	32	36	32	33	39	44	41	42	20	22	37	37
	Left	27	31	30	32	40	43	37	38	27	30	43	43
Dynamometer (hands)	Right	35	8	37	5	44	5	44	2	27		47	
	Left	30		33	2	36	8	37		26	8	38	8

* Periods of therapy separated by an interval of three months

medication there was a definite increase in strength generally, but the patient had many somatic complaints. During the period of combined aminoacetic acid and ephedrine medication improvement in muscular strength persisted, but the psychoneurotic manifestations continued. The patient showed a distaste for aminoacetic acid and would refuse this form of medication. During the period of medication with anterior pituitary extract there was a marked exacerbation of weakness associated with paroxysmal choking. The administration of prostigmine hypodermically resulted in marked increase in muscular strength but was accompanied by objectionable features, such as muscle contractions, diarrhea and burning on urination. As a result the patient rejected this form of medication and preferred to continue with ephedrine until her discharge from the hospital on May 28, 1936.

Comment—This patient had pernicious anemia in addition to myasthenia gravis. She was also obviously psychoneurotic. The objective results of therapy are shown in table 4. The tests were not entirely satisfactory in this case, owing to lack of cooperation. Nevertheless,

ephedrine was shown to be effective by means of the dynamometer. The ineffectiveness of anterior pituitary extract and the comparatively striking beneficial effect of prostigmine are clearly demonstrated.

CASE 5—S S, a white girl aged 13 years, was admitted to the Montefiore Hospital on Feb 22, 1935, with a history of gradual onset of hoarseness and difficulty in swallowing in the autumn of 1933. Soon afterward excessive fatigability appeared and was accompanied by diplopia, drooping of the eyelids and nasal speech. All of these symptoms improved slightly after a course of nonspecific protein therapy and then became worse. Weakness was always more marked in the evening than in the morning.

Physical examination on admission revealed the girl to be markedly undernourished. She was of asthenic habitus. There were generalized muscular weakness with rapid fatigability, particularly in the upper extremities, typical myasthenic

TABLE 5—*Results of Therapy in Case 5*

		Medicament													
		None		Amino acetic Acid		Ephe drine		Amino acetic Acid* Plus Ephedrine		Anterior Pituitary Extract* (Hypo)		Prostig mine (Hypo)		Prostig mine (Hypo) Plus Ephedrine	
Tongue		40	30	47	32	50	42	52	45	33	26	31	38	100	1 22
Arms (static)	Right	33		22		43		53		02		55		1	12
	Left	30		22		39		43		01		53			50
Arms (dynamic)	Right	38	47	40	1 00	52	1 10	50	1 10	17	23	66	1 31	70	1 43
	Left	35	45	36	48	50	1 04	47	1 06	14	21	57	1 17	57	1 17
Legs (static)	Right	47		1 15		1 08		1 10		10		1 24		2	20
	Left	50		1 18		1 12		1 02		08		1 12		1	45
Legs (dynamic)	Right	30	33	38	43	38	42	50	52	17	20	54	1 05	70	1 20
	Left	33	35	45	50	40	47	46	45	15	17	54	1 00	53	58
Dynamometer (hands)	Right	16		18 5		19 2		19 5		14 7		25 5		27 5	
	Left	14 7		17 5		18 5		18 5		9 5		24 2		25 7	

* Periods of therapy separated by an interval of five months.

facies, bilateral ptosis, particularly on the right, multiple extraocular muscular pareses, and weakness of the muscles of mastication and those of the palate and tongue. Early fatigability with rapid recovery on resting was demonstrable in all the paretic muscles.

Laboratory Data—Urinalysis gave negative results. The blood count was within normal limits. The value for blood sugar was 93 mg, that for urea nitrogen 9.3 mg, that for calcium 10.9 mg and that for phosphorus 5.2 mg, per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid revealed no evidence of syphilis. The basal metabolic rate was -11 per cent. The electrocardiogram showed sinus rhythm with low voltage.

Course—During the initial period without medication the condition of the patient remained unchanged. During the period of aminoacetic acid medication there was no change in her condition. In spite of a special diet there was no increase in weight, largely because of the rather marked dysphagia. During the period of ephedrine medication there was a definite increase in muscular strength, which was greater objectively than subjectively. During the period of combined

ephedrine and aminoacetic acid medication improvement continued, and the patient was discharged on July 28, 1935. After her readmission on December 17 there was an exacerbation of muscular weakness accompanied by dyspnea and dysphagia during the period of medication with anterior pituitary extract. After the administration of prostigmine hypodermically there was a considerable increase in strength generally, but this could be maintained only by frequent administration of this medicament. The patient gradually became weaker but was fairly comfortable except for considerable difficulty in swallowing mucus. On March 19, 1936, there was a sudden onset of marked dyspnea. Examination revealed a massive collapse of the left lung, and death occurred on March 20, 1936. In the terminal stage prostigmine for a time was remarkably effective in relieving the patient temporarily, but finally it became ineffective.

- *Comment*—The age of onset of disease (11 years) in this patient is unusual. Only a few cases of myasthenia gravis have been reported as occurring in children. The occurrence of massive pulmonary collapse deserves mention as an unusual complication which should be guarded against in the case of a patient with marked dysphagia. The objective results of therapy in this case are shown in table 5. The partial benefit resulting from ephedrine therapy is best shown in tests of the upper extremities. Although the patient was in a state of relapse, the complete ineffectiveness of anterior pituitary extract and, in contrast to this, the remarkable effectiveness of prostigmine are strikingly demonstrated. Combined prostigmine and ephedrine medication apparently produces a slightly better result than does the former medication alone.

CASE 6—W. K., a man aged 29 years, a dress cutter, was admitted to the Montefiore Hospital on April 17, 1936. About thirteen years previously he had begun to notice diplopia and drooping of the right upper eyelid. At about the same time he noted excessive fatigue after an ordinary day's activity. He also had difficulty in swimming and was unable to play baseball as previously. His condition remained unchanged for four years, and then weakness became more marked. Dysphagia with nasal regurgitation of fluids appeared at that time. He was admitted to another hospital in 1926, where he was given ephedrine medication, and this was continued. However, all symptoms have persisted so that the patient has been unable to work for the past seven years.

The significant physical findings on admission were marked weakness of all the body musculature with rapid fatigability, more marked in the extremities and more marked proximally than distally, atrophy of the paretic musculature of the shoulder girdle, myasthenic facies and weakness of the jaw muscles, weakness and atrophy of the tongue, and multiple extraocular muscle pareses, particularly in the right eye.

Laboratory Data—A urinalysis and a blood count gave results within normal limits. The value for blood sugar was 96 mg, that for urea nitrogen 17.6 mg, that for calcium 9.4 mg and that for phosphorus 4.3 mg per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid revealed no evidence of syphilis. The basal metabolic rate was -12 per cent. The electrocardiogram showed marked

sinus arrhythmia. A myasthenic electrical reaction was obtained in the muscles of the right side of the face and in those of the right forearm.

Course—During the initial period without medication there was an exacerbation of symptoms. The patient was unable to wash himself, he could walk only a very short distance, he could not raise a spoon to his mouth, he showed rapid fatigability in his speech and marked dysphagia, he could not smile, shut his eyes or whistle, and he had diplopia and complained of difficulty in evacuation of the bowel. During the period of ephedrine medication there was a gradual and considerable improvement in his strength, particularly in the extremities. This was manifested in a diminution in the intensity of many of the aforementioned manifestations. After the administration of prostigmine hypodermically there was profuse perspiration after ten or fifteen minutes and then an increase in motor power, first in the face. A maximum effect was observed at the end of one and one-half hours (fig. 2). At this time the patient would be able to smile and

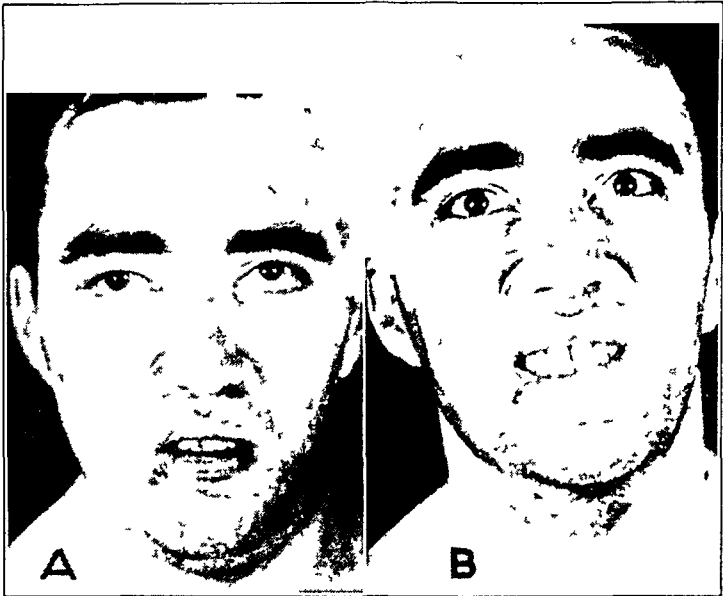


Fig. 2 (case 6)—Facial appearance of the patient (A) without medication and (B) after hypodermic administration of prostigmine.

TABLE 6—Results of Therapy in Case 6

		Medicament									
		None		Ephedrine		Ephedrine Plus Prostigmine (Hypo)		Prostigmine (8 Tablets)		Prostigmine (8 Tablets) Plus Ephedrine	
Tongue		60	24	60	25	120	1 00	77	37	105	50
Arms (static)	Right			10		1	07	12		19	
	Left						58	15		23	
Arms (dynamic)	Right			5	05	37	55	7	11	19	32
	Left			1	02	35	50	4	07	17	28
Legs (static)	Right	18		32		1	40	35		48	
	Left	20		36			1 18	37		52	
Legs (dynamic)	Right	39	32	44	35	160	2 20	40	33	83	1 16
	Left	45	35	47	33	200	2 25	49	38	87	1 26
Dynamometer (hands)	Right	24	2	45		78	8	41	2	77	2
	Left	25		44	5	70	2	45	5	76	2

close his eyes tightly and whistle. He would notice slight borborygmus and would be apt to have a bowel movement at this time. During the period of oral administration of prostigmine the muscular strength of the patient continued to manifest improvement, which, however, was dependent on continued administration of this drug, so that during the night there was often marked weakness. During the period of combined ephedrine and prostigmine medication the only subjective alteration consisted of a possibly more prolonged beneficial effect following each dose.

Comment—The objective results of therapy in this case are shown in table 6. Ephedrine apparently shows its greatest effect in the extremities. Prostigmine was remarkably beneficial throughout, and striking results were obtained when it was administered hypodermically. Com-

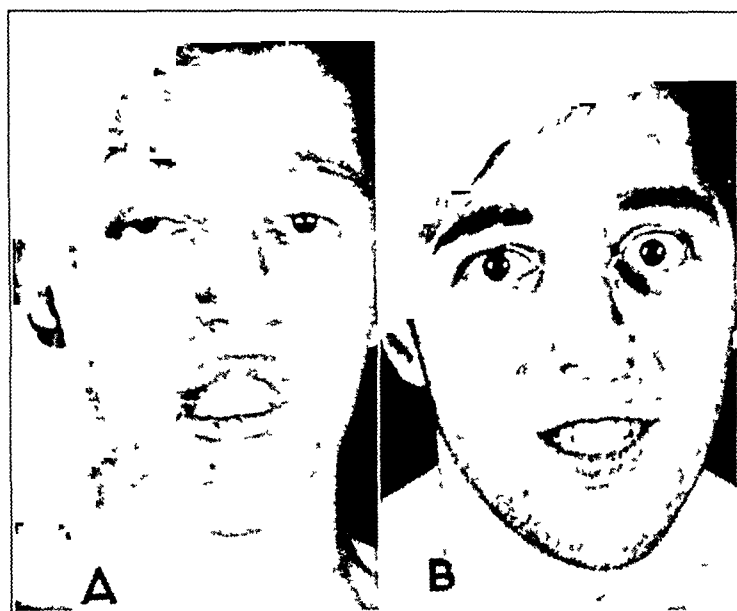


Fig 3 (case 7)—Facial appearance of the patient (A) without medication and (B) after hypodermic administration of prostigmine

bined prostigmine and ephedrine therapy by mouth seems to be considerably more effective than administration of either of these medicaments alone.

CASE 7—H. L., a man aged 20 years, a law student, was admitted to the Montefiore Hospital on Sept. 9, 1935. He had had poliomyelitis at 1 year of age, with residual weakness of the right leg. Subsequently he was in good health until the sudden onset of his present illness in May 1935, when he noticed blurring of vision while taking a law examination. This symptom recurred and rapidly became more marked. It was soon followed by the appearance of drooping of the eyelids and occasional diplopia. One month later weakness of both legs appeared, followed by weakness of the right arm and then of the left arm. At the same time difficulty in chewing was noted. Weakness rapidly became more marked, the patient becoming bedridden shortly before his admission to the hospital.

The significant physical findings on admission were a sallow complexion, with some greasiness of the skin, bilateral foot drop, marked generalized motor weakness, more in the right upper extremity than in the left and increasing caudally to almost a total paralysis of both lower extremities, rapid fatigability of the paretic muscles, muscular atrophy in the right lower extremity but nowhere else, absence of the deep reflexes in the lower extremities, bilateral external ophthalmoplegia, bilateral ptosis, a myasthenic facies, and weakness of the jaw muscles

Laboratory Data—Urinalysis gave negative results. The blood count was within normal limits. The value for blood sugar was 86 mg, that for urea nitrogen 12.5 mg, that for calcium 12.2 mg and that for phosphorus 5.2 mg per hundred cubic centimeters. Serologic tests of the blood and of the spinal fluid revealed no evidence of syphilis. The basal metabolic rate was -14 per cent. The electrocardiogram showed right axis deviation.

Course—During the initial period without medication there were increasing weakness and an episode of excessive drowsiness, with constant yawning lasting

TABLE 7—Results of Therapy in Case 7

		Medicament									
		None		Aminoacetic Acid Plus Ephedrine		Aminoacetic Acid Plus Ephedrine Plus Prostig- mine (Hvpo)		Prostig- mine (11 Tablets)		Prostigmine (11 Tab- lets) Plus Ephedrine	
Arms (dynamic)	Right					10	15			2	04
	Left					18	33			4	07
Forearms (dynamic)	Right	10	17	16	31	100	2 23	13	23	21	38
	Left	32	40	41	1 10	100	2 03	40	1 07	100	2 13
Toes (dynamic)	Right	30	26	50	37	62	52	48	35	52	35
	Left	47	35	63	45	110	1 38	60	40	76	45
Dynamometer (hands)	Right					8				4	2
	Left			1	2	15				8	2

several days. Paroxysmal attacks of dyspnea appeared. Because of the seriousness of the symptoms, combined ephedrine and aminoacetic acid medication was instituted. He gradually showed improvement manifested by less marked fatigability and a quicker return of strength after activity. However, there was hardly any noticeable effect on the muscular strength of the lower extremities. Paroxysmal dyspnea still occurred, but less frequently. Within ten minutes after the administration of prostigmine hypodermically the patient would experience a generalized tingling in the muscles, and shortly afterward he would be able to raise his eyelids. The maximum effect would be obtained after forty-five minutes, and the duration of the effect approximated four hours. There was an improvement in muscular strength generally, but particularly in the distribution of the cranial nerves (fig 3). Slight motion of the eyes as well as slight motion of the legs was possible during the optimum phase of improvement. During the period of oral administration of prostigmine improvement in muscular strength was also achieved, although it was less noticeable than after hypodermic administration of this drug. Evacuation of the bowel could be accomplished easily, in contrast with the difficulty noticed immediately after admission. During the period of combined prostigmine and ephedrine medication the patient subjectively seemed to experience a more prolonged beneficial effect following each dose of the former drug.

Comment—The rapidity of progression and the intensity of involvement are unusual features. The existence of bilateral external ophthalmoplegia is also noteworthy. The objective results of therapy are shown in table 7. Myasthenia was not demonstrable by means of the dynamic lingual test, this test was therefore omitted. Combined aminoacetic acid and ephedrine therapy was mildly beneficial, and it is likely that this result was essentially due to the ephedrine. Prostigmine given by mouth produced an approximately equivalent result in the extremities but was more effective than ephedrine in relieving bulbar manifestations (not measured objectively). Prostigmine administered hypodermically was strikingly effective, in view of the almost complete incapacitation. This is well shown in table 8. The oral administration of both prostigmine and ephedrine seemed to be more beneficial than administration of the former medicament alone.

TABLE 8—*Effect of Prostigmine (3 Ampules Hypodermically) in Case 7*

Hour	Right				Left			
	9	10	11	1	9	10	11	1
Dynamometer	0	36	25	3	0	45	36	5
	0	40	28	0	0	50	37	0
	0	35	22	0	0	54	25	0
	0	30	15	0	0	42	20	0
	0	35.2	22.5	0.7	0	47.7	29.5	1.2

GENERAL COMMENT

The treatment of myasthenia gravis has always more or less reflected the varying theories as to the pathogenesis of this disease. It is therefore pertinent to mention briefly some of these theories. For many years the condition was considered to be primarily a neurologic disorder, but no characteristic lesions were ever discovered in either the central or the peripheral nervous system. Later the discovery of lymphoid changes caused emphasis to be placed on the muscles as the primary site of disease. Subsequently the observation of an enlarged thymus gland in about 50 per cent of cases directed attention to the endocrine system.

Throughout this period, which lasted until 1930, a wide variety of remedies were used, and conflicting results were often reported. As in all debilitating diseases, tonics were extensively employed, strychnine in massive doses was particularly recommended. Diet therapy was tried by some observers, and the administration of calcium was suggested by others. Endocrine therapy of all types was resorted to, the disease being considered due to endocrine dysfunction. Beneficial effects and

complete ineffectiveness were reported by various observers as following the use of adrenal, thymic, thyroid, ovarian, testicular and hypophyseal preparations

Recently Simon⁴ has described 2 cases in which subsidence of symptoms occurred after the administration of anterior pituitary extract. The present study showed a complete lack of favorable response in every case in which this aqueous solution of the adenohypophysis was used (tables 3 to 5)

Of all the forms of therapy discussed thus far, none have stood the tests of time and repeated trials. Irradiation of the thymus in cases in which this gland is enlarged has been reported as successful in a few instances but is usually ineffective. It should be emphasized that symptomatic treatment, consisting of such measures as rest, nourishing diet and good nursing care, has always been used and still is to be used in conjunction with the more specific forms of therapy.

In recent years it has been gradually recognized that a disturbance of muscle metabolism exists in myasthenia gravis. The discovery of creatine in the urine of some patients was considered as evidence in favor of such a hypothesis. In 1932, Remen⁵ and Boothby⁶ reported amelioration of symptoms following the administration of aminoacetic acid. Shortly before this time, Edgeworth⁷ demonstrated the beneficial effect of ephedrine. Subsequently, Boothby⁸ recommended the use of combined aminoacetic acid and ephedrine medication as more effective than the use of either remedy alone.

The present investigation indicates that aminoacetic acid alone is of little or no value (tables 1 to 5). The value of the test procedures utilized in this study is well illustrated in 1 case (case 1). The patient stated definitely that he felt stronger while receiving aminoacetic acid, but this subjective improvement was not demonstrated in the results of the objective test (table 1). It was just such gross unreliability that this study avoided by its manner of investigation.

Ephedrine medication alone was shown to be capable of producing considerable improvement in some cases (tables 1, 2, 3 and 6). In 2 cases the objective evidence of improvement could not be considered

4 Simon, H. E. Myasthenia Gravis, *J. A. M. A.* **104** 2065 (June 8) 1935

5 Remen, L. Zur Pathogenese und Therapie der Myasthenia gravis pseudo-paralytica, *Deutsche Ztschr. f. Nervenheilk.* **128** 66, 1932

6 Boothby, W. M. Myasthenia Gravis. A Preliminary Report on the Effect of Treatment with Glycine, *Proc. Staff Meet., Mayo Clin.* **7** 557 (Sept. 28) 1932

7 Edgeworth, H. A Report of Progress on the Use of Ephedrine in a Case of Myasthenia Gravis, *J. A. M. A.* **94** 1136 (April 12) 1930

8 Boothby, W. M. Myasthenia Gravis. The Effect of Treatment with Glycine and Ephedrine, *Arch. Int. Med.* **53** 39 (Jan.) 1934

significant (tables 4 and 5) It would appear from this study that the good results obtained with combined aminoacetic acid and ephedrine medication are probably largely if not entirely attributable to the latter remedy alone This is most strikingly shown in 2 instances (tables 1 and 3) The dynamic arm test in these 2 cases seemed to indicate relatively greater benefit resulting from combined medication, but confirmation was lacking in the other test procedures

It is interesting to note that ephedrine apparently is more effective in improving the motor power of the appendicular skeletal muscles than that of the musculature innervated by the cranial nerves In 3 patients the dynamic lingual test showed no significant evidence of benefit, which contrasted with the results of other tests (tables 1, 3 and 6) In only 1 case (table 2) did the dynamic lingual test show significant change with ephedrine therapy No satisfactory explanation is available for the relatively greater beneficial effect of ephedrine on the muscles innervated by the spinal nerves

Although the use of ephedrine constituted a great advance in the treatment of myasthenia gravis, within five years it was followed by an even greater therapeutic contribution This is directly attributable to the striking advances made in knowledge regarding the chemical agents concerned in the transmission of nervous impulses Fundamental work in this field done separately by Dale⁹ and Loewi,¹⁰ as well as more recent research, indicate that acetylcholine is liberated on stimulation of the motor nerves supplying striated muscles It has also been discovered that physostigmine enhances and prolongs muscle contraction, apparently by inhibiting the destructive action of choline esterase on acetylcholine These phenomena have focused attention on the myoneural junction as the probable site of the pathologic process in myasthenia gravis

In 1934, Walker¹¹ reported definite improvement following the use of physostigmine in a case of myasthenia gravis Subsequently¹² a synthetic analogue known as prostigmine (dimethylcarbamate ester of 3-hydroxyphenyltrimethylammonium methylsulfate) replaced physostigmine as the remedy of choice owing to its less toxic side effects Numerous reports in the literature have demonstrated the remarkable

9 Dale, H Chemical Transmission of the Effects of Nerve Impulses, *Brit M J* **1** 835 (May 12) 1934

10 Loewi, O Ferrier Lecture on Problems Connected with the Principle of Humoral Transmission of Nervous Impulses, *Proc Roy Soc, London, s B* **118**: 299 (Sept 2) 1935

11 Walker, M B Treatment of Myasthenia Gravis with Physostigmine, *Lancet* **1** 1200 (June 2) 1934

12 Pritchard, E A B The Use of "Prostigmin" in the Treatment of Myasthenia Gravis, *Lancet* **1** 432 (Feb 23) 1935

effectiveness of this remedy. This improvement is so uniformly observed that the injection of prostigmine in case of doubt has been proposed by Viets and Schwab¹³ as a diagnostic procedure. However, it should be remembered that prostigmine causes no permanent cure, as with insulin in diabetes, continued administration is required. Progression of the disease process may result in death despite the use of prostigmine, as occurred in case 5 and as has been reported by Laurent and Walker¹⁴.

The present study confirms in all essential respects the many favorable reports concerning the effectiveness of prostigmine. Both the parenteral and the oral mode of administration produce excellent results, and the latter method is naturally preferable. The effect of a single dose persists for only a few hours (table 8), and therefore the drug must be given at relatively frequent intervals, usually three times a day. The degree of benefit resulting from the use of prostigmine varies greatly in different patients, and the most striking improvement is demonstrable when the drug is administered hypodermically. In contrast with the relative lack of effectiveness observed in the tongue when ephedrine is used (see foregoing sections) the noticeable benefit resulting from prostigmine is easily and often most clearly demonstrated by means of the dynamic lingual test (tables 3 to 6).

The results obtained in this study seem to indicate that combined prostigmine and ephedrine medication is more effective than use of the former remedy alone (tables 5 to 7). The combination increases both the intensity and the duration of the beneficial effect obtained from each dose of prostigmine. The combined administration of prostigmine and ephedrine is therefore recommended as the most satisfactory treatment available. The use of both these remedies has also been suggested by Boothby,¹⁵ Laurent and Walker¹⁴ and Macfarlane¹⁶.

The use of large doses of potassium chloride has been proposed by Laurent and Walther¹⁷ as an adjuvant to prostigmine in the treatment of myasthenia gravis. Such therapy was tried in case 7 and was beneficial in that the effect of prostigmine seemed to be prolonged. How-

13 Viets, H. R., and Schwab, R. S. Prostigmin in the Diagnosis of Myasthenia Gravis, *New England J. Med.* **213** 1280 (Dec 26) 1935. Schwab, R. S., and Viets, H. R. Prostigmin Test in Myasthenia Gravis, *ibid.* **219** 226 (Aug 18) 1938.

14 Laurent, L. P. E., and Walker, M. B. Prostigmin and Its Analogues in Myasthenia Gravis, *Lancet* **1** 1457 (June 27) 1936.

15 Boothby, W. M. Myasthenia Gravis, *Tr. A. Am. Physicians* **51** 188, 1936.

16 Macfarlane, J. W. Myasthenia Gravis: Its Treatment by Combination of Prostigmin and Glycine-Ephedrine Therapy, *Glasgow M. J.* **128** 7 (July) 1937.

17 Laurent, L. P. E., and Walther, W. W. Influence of Large Doses of Potassium Chloride on Myasthenia Gravis, *Lancet* **1** 1434 (June 22) 1935.

ever, during this period there occurred unpredictable episodes of toxic manifestations

It is interesting to note that the tests utilized in this investigation often apparently revealed the varying degree of myasthenic disease in different parts of the body musculature in each patient. This was shown by a selective lack of response to medication. For example, in 1 instance (table 4) the motor power in the legs showed no response to medication other than that which might represent a generalized weakness. In another instance (table 7) the preponderance of involvement on the right side was clearly indicated. However, one must be careful in interpretation of such varying degrees of response to medication, since a lack of response in a particular part may be due either to a localized relative sparing of musculature or to a localized relative preponderance of permanent weakness as compared with the more characteristic transient weakness which may exist in other groups of muscles. The latter element in myasthenia gravis, namely, transient weakness, may be the one which is responsive to specific medication and may therefore determine the relative value of therapy for each patient.

SUMMARY AND CONCLUSIONS

A number of reliable test procedures devised for the measurement of muscular strength and fatigability are described. In a group of 7 patients with myasthenia gravis these tests have been utilized for an objective evaluation of therapy in this disease. The various medications administered were anterior pituitary extract, aminoacetic acid, ephedrine, combined aminoacetic acid and ephedrine, prostigmine and combined prostigmine and ephedrine.

This investigation leads to the following conclusions regarding therapy in myasthenia gravis: 1. Antuitrin and aminoacetic acid are ineffective remedies. 2. Ephedrine is definitely beneficial and is probably responsible for the good results obtained with combined aminoacetic acid and ephedrine medication. 3. Prostigmine is a remarkably effective remedy, and its value is enhanced when administered together with ephedrine. 4. The most satisfactory form of therapy in the absence of toxic manifestations consists of the oral administration of combined prostigmine and ephedrine medication.

ATROPHIC GASTRITIS GASTROSCOPIC STUDIES ON THE EFFECTS OF LIVER AND IRON THERAPY

PRELIMINARY REPORT

RUDOLF SCHINDLER, M D

JOSEPH B KIRSNER, M D

AND

WALTER LINCOLN PALMER, M D

CHICAGO

Chronic atrophic gastritis constitutes 13.6 per cent of gastric diseases. It is found constantly in cases of pernicious anemia, sprue and combined coid degeneration and in many cases of gastric carcinoma, in which it apparently precedes the development of the tumor. However, atrophic gastritis occurs without associated diseases and appears to be a primary disease entity. The cause is unknown, in some cases the disease follows acute corrosive gastritis (such as that from acids or lyes), but most often chronic superficial gastritis precedes its development.

The gross anatomic features of this condition are best observed through the gastroscope. The gastric mucosa is not the orange-red of the normal mucosa but grayish pink, gray or greenish gray. It may be so thinned that the blood vessels of the submucosa become visible as blue or red arborizations. The atrophic changes are present either as sharply limited patches or as diffuse atrophic areas, which may involve the entire gastric mucosa. These changes usually are more extensive and more severe in the upper portions of the stomach. My associates and I believe that this atrophy represents an inflammatory rather than a merely degenerative process. The evidence in support of this concept will be published elsewhere.

Microscopically the outstanding feature is the thinness of the gastric mucosa, the diameter of which may be reduced to one fourth of its normal size. This thinning is due to the disappearance of the gastric glands. In the cases of most severe involvement the glands disappear completely. Remnants of crypts lie in a dense, chiefly lymphocytic, interstitial infiltration. The epithelium of these remnants of glands, as

From the Department of Gastroenterology, The School of Medicine of the Division of the Biological Sciences, University of Chicago

well as the surface epithelium, presents characteristic changes. In many places the normal gastric epithelium is transformed into an intestinal type of epithelium containing many goblet cells. Inflammatory changes of the submucosa and muscularis are observed even in cases of the most complete atrophy. Edema and cellular infiltration of these layers are frequent. If the atrophy is incomplete, the thickness of the gastric mucosa is not uniform. In some sections many normal gastric glands are still found, while no glands are seen in other areas, as shown in the accompanying illustration. It would seem that such atrophic changes represent the end stage of a severe inflammation and that mucosal regen-



Microscopic section of the gastric mucosa in a case of severe atrophic gastritis. The thickness of the mucosa is not uniform. The diameter at the right side is about one third and on the left side about one half its normal thickness. The normal glands are almost completely missing. The surface epithelium and the remnants of the glands contain goblet cells. There is a large amount of interstitial infiltration.

eration could not occur. However, hyperplastic proliferative nodes and pseudopolyps have been observed in some cases, evidently representing compensatory reactions of the gastric mucosa to the atrophy. Complete regeneration of the gastric mucosa to its previously normal state has never been observed without treatment. The atrophic changes in the cases of more severe involvement either remain stationary or progress

Jones, Benedict and Hampton¹ were the first to observe and describe apparently complete regeneration of the gastric mucosa after liver therapy in a case of atrophic gastritis associated with pernicious anemia. As seen gastroscopically, the mucosa reassumed its normal thickness, the characteristic gray was replaced by the normal orange-red, the blood vessels of the submucosa became invisible and the entire gastric mucosa was indistinguishable from the normal. This important observation later was confirmed by Chevallier and Moutier,² by Lehmann,³ by Schiff and Goodman,⁴ by Schindler⁵ and by Schindler and Serby.⁶ The last two authors emphasized the fact that the apparent regeneration does not occur in all cases of treated pernicious anemia, for they observed lack of improvement and even progression of the atrophy despite energetic treatment.

Chevallier and Moutier² probably were the first to describe cases of atrophic gastritis without pernicious anemia in which the same result, i. e. apparent regeneration of the atrophic mucosa after liver therapy, was obtained. A similar case was reported by Schindler and Serby,⁶ who suggested that in some cases atrophic gastritis may be the result of a lack of the antianemic factor without concomitant changes in the blood and also that a parallelism between atrophy of the tongue, of the pharynx and of the stomach and changes in the cord should be assumed. Furthermore, Chevallier and Moutier² found that atrophic gastritis was present in some cases of hypochromic anemia and that in several of these the atrophic changes disappeared after iron therapy. This observation has been recently confirmed by Schiff.

The evidence seems to indicate, therefore, that atrophic gastritis, in some cases at least, is related to a deficiency state.

There is no available information to indicate whether this apparently complete regeneration, as seen gastroscopically, is a true histologic regeneration. There have been no microscopic studies in cases in which the gastric mucosa became normal after liver therapy. It is to be hoped that such observations will be made in the future. Brown found in cases of treated pernicious anemia that the gastric mucosa examined at necropsy

1 Jones, C. M., Benedict, E. B., and Hampton, A. O. Variations in Gastric Mucosa in Pernicious Anemia, *Am J M Sc* **190** 596, 1935.

2 Chevallier, P., and Moutier, F. La gastroscopie dans les maladies du sang, *Sang* **11** 935, 1937.

3 Lehmann, R. Les atrophies gastriques dans les anémies idiopathiques et les métanémies, Paris, E. François, 1936.

4 Schiff, L., and Goodman, S. Chronic Gastritis. Present Day Status, *Ohio State M J* **34** 1220, 1938.

5 Schindler, R. Gastroscopy. The Endoscopic Study of Gastric Pathology, Chicago, University of Chicago Press, 1937.

6 Schindler, R., and Serby, A. M. Gastroscopic Observations in Pernicious Anemia, *Arch Int Med* **63** 334 (Feb) 1939.

showed no changes from the usual appearance associated with the untreated disease. It is possible that in these cases no regeneration would have been seen at gastroscopic examination. However, the fact remains that the living gastric mucosa in cases in which there has been a response to sufficient treatment cannot be distinguished from a normal mucosa. This observation has led us to employ systematic substitution therapy in 8 cases of atrophic gastritis not associated with pernicious anemia, combined cord degeneration, spinae or pellagra. Only cases were chosen in which the gastroscopic appearance was marked and in which repeated gastroscopic examinations were possible. The developments in case 1 are reported as control observations in a case of untreated atrophic gastritis. In the subsequent 8 cases, to be presented briefly, the effect of substitution therapy on the gastroscopic picture alone is given chief emphasis. The clinical reaction to this treatment will not be described, since spontaneous remissions of symptoms, sometimes of long duration, are frequent in this disease. Cases 2, 3 and 4 are instances of severe atrophic gastritis in which substitution therapy was unsuccessful. In cases 5 to 8 liver therapy led to the apparent regeneration of the gastric mucosa previously described. In case 9 liver therapy was unsuccessful, while treatment with iron was followed by mucosal regeneration.

REPORT OF CASES

CASE 1—*Atrophic gastritis not treated with substitution therapy*

A 66 year old Irish woman was first seen on Oct 4, 1937, with the complaints of epigastric pain and marked weakness of ten to fifteen years' duration. Her condition had been diagnosed elsewhere as gastric ulcer, although no ulcer was demonstrated on roentgen examination. Her pain usually was relieved by warm liquids, the relief from alkalis was only temporary. At the time of examination she was thin and appeared weak. The thyroid gland was enlarged and nodular, but otherwise the examination gave negative results.

Gastric analysis after an Ewald test meal showed free hydrochloric acid and total acidity 32. The histamine test, with 0.5 mg, showed free hydrochloric acid 28. The stools did not contain any occult blood.

The hemoglobin content was 79 per cent, and the red blood cell count 4,710,000.

Roentgenograms showed that the gallbladder, esophagus and stomach were normal but that there were two diverticula of the second portion of the duodenum.

The course of the disease was characterized by remissions and relapses of symptoms. In December 1937 the patient stated that she had not felt better in many years. In June 1938, however, her symptoms recurred.

Gastroscopic examination on Oct 22, 1937, disclosed that in the midportion and the upper portion of the stomach the mucosa was thinned and gray and contained some blood vessels. The impression of atrophic gastritis of the upper portions of the lesser curvature and anterior wall was given. On June 24, 1938, in the midportion of the stomach extensive atrophy was seen involving the lesser curvature

the anterior wall and the greater curvature. The mucosa was gray and appeared thinner than normal. Patchy atrophic areas were observed in the upper portion of the stomach.

The impression was of atrophic gastritis of the upper portions of the stomach.

This was a typical case of atrophic gastritis not treated by substitution therapy. Gastroscopic check eight months after the initial gastroscopic examination showed no essential change in the mucosa, although the patient improved clinically with a bland diet and sedatives.

CASE 2—Atrophic gastritis not influenced by liver therapy

A 56 year old Italian man was first seen on July 21, 1937, complaining of gas, belching and a salty bitter taste in his mouth, all of three years' duration, he also complained of having had substernal and epigastric pain for four to five months. He had lived chiefly on bread and milk for two years, the epigastric pain, however, was not related to the taking of food. His condition had been diagnosed elsewhere as gastric ulcer and gallbladder disease. The physical examination gave essentially negative results.

Gastric analysis after an Ewald test meal showed free hydrochloric acid 0 and total acidity 6. Two histamine tests, each with 0.5 mg (Nov 3, 1937, and Feb 19, 1938), revealed no free hydrochloric acid. The hemoglobin content varied between 84 and 92 per cent and the red blood cell count between 4,560,000 and 5,000,000.

Roentgenograms revealed a normal gallbladder, esophagus, stomach and duodenum.

From Nov 13 to Dec 31, 1937, the patient received at approximately weekly intervals intramuscular injections of Lederle's liver extract⁷ in 1 cc amounts for a total of 8 cc. On Nov 3, 1937, gastroscopic examination disclosed that the antrum and the pylorus were normal. Above the musculus sphincter antri the mucosa of the anterior wall was thin and gray and the blood vessels were visible. Patchy areas of redness with adherent mucus were seen in the highest portion of the stomach. The impression gained was of atrophic gastritis of the anterior wall of the body of the stomach and mild chronic superficial gastritis of the fornix of the stomach. At gastroscopic examination on Jan 1, 1938, the antrum and the pylorus appeared normal. The mucosa of the body, especially of the anterior wall, of the greater curvature and of the posterior wall, was thin and gray and contained an extensive network of branching blood vessels. Patches of adherent mucus were observed in the highest portions of the stomach. The impression gained was of chronic superficial and atrophic gastritis. The atrophic gastritis became more extensive, and no effect of the liver therapy was noted.

The atrophic gastritis in this case did not respond to liver therapy, in fact the condition became more extensive.

CASE 3—Atrophic gastritis not influenced either by non therapy or by liver therapy

A 44 year old white sheet metal worker when admitted to the hospital on April 28, 1937, stated that for eighteen months he had experienced attacks of epigastric pain for periods of two weeks followed by short remissions. The pain occurred usually two to four hours after meals and was relieved by food or powders. He had lost 18 pounds (8.2 Kg) during this time. In addition, he

⁷ The concentrated extract was used.

complained of having had soreness under the right costal border associated with nausea for four years. He had been weak and dizzy for two weeks prior to his admission. Physical examination gave negative results except to reveal tenderness in the epigastrium.

Gastric analysis after an Ewald test meal (May 4, 1937) and two histamine tests, each with 0.5 mg (June 12, 1937, and July 2, 1938), revealed no free hydrochloric acid. The stools contained no occult blood. The blood count on seven occasions was normal.

Roentgenograms revealed that the esophagus, stomach, duodenum and gallbladder were normal. The clinical course was uneventful. The patient's improvement began on June 12, 1937, and continued until July 10, 1938, although he did not receive specific substitution therapy during this period. However, he stated that he felt particularly well after receiving liver therapy. Seven gastroscopic examinations were performed. Between the third and fourth observations (Aug 8 and Sept 9, 1937) the patient received 0.8 Gm of ferrous sulfate daily. Between the fourth and sixth examinations (Sept 22, 1937, and Jan 15, 1938) he received at weekly intervals fifteen intramuscular injections, each of 1 cc of Lederle's liver extract. Additional liver extract was given at two week intervals from Jan 28 to May 4, 1938 in 1 cc amounts, until a total of 6 cc was given.

On June 2, 1937, the mucosa of the antrum, the anterior wall and the lesser curvature of the body of the stomach presented pinkish nodes. Several gray patches, apparently thinned mucosa, were seen below the cardia, one of these contained small red blood vessels. An impression of diffuse chronic gastritis and beginning atrophy in the upper portions of the stomach was received. On June 23 the nodes had disappeared, but thin gray mucosa with visible blood vessels was observed in the highest portion of the stomach, which gave the impression of atrophic gastritis. On August 11 large areas of thin gray mucosa with blood vessels were visible in the body of the stomach, giving an impression of progressive atrophic gastritis. After this examination, iron therapy, as previously mentioned, was started. On September 10 large portions of the lesser curvature and of the fornix presented a thin smooth gray mucosa containing a net of blood vessels, which gave the impression of extensive atrophic gastritis with further progression in spite of the iron therapy. The administration of iron therefore was discontinued and liver therapy instituted. On November 24 the atrophic gastritis was unchanged. On Feb 18, 1938, there was extensive atrophic gastritis with visualization of thick blue blood vessels. One small grayish yellow erosion was noted in the anterior wall. No liver therapy was given for two months prior to the examination on July 29, 1938, at which time the greater curvature of the antrum, the entire anterior wall and the lesser curvature of the stomach were completely atrophic. Only scattered portions of the posterior wall still presented a normal mucosa.

In this case the progression of atrophic gastritis over a period of fifteen months was observed in a total of seven gastroscopic examinations. It is obvious that neither iron nor liver therapy had any marked effect on the condition of the gastric mucosa.

CASE 4—Atrophic gastritis not influenced by liver, ascorbic acid, nicotinic acid or vitamins

A 53 year old laborer when first seen, on June 1, 1938, stated that he had been markedly weak and fatigued and had lost his appetite after a tonsillectomy performed in February 1938. The physical examination gave negative results except to reveal the usual physical signs of bronchial asthma.

The hemoglobin content of the blood varied from 70 to 90 per cent and the red cell count from 4,140,000 to 4,800,000. No occult blood was found in the stools. Gastric analysis after an Ewald test meal on June 10 and a histamine test, with 0.5 mg., on June 13, showed no free hydrochloric acid. However, histamine tests, each with 0.6 mg., on July 27 and 29 and August 12 revealed, respectively, 32, 38 and 30 units of free hydrochloric acid. Histamine tests, with 0.6 mg., on September 3 and 18 again showed no free hydrochloric acid. Histamine tests, with 0.6 mg., on Oct. 3 and 28, 1938, and March 8, 1939, demonstrated 20, 28 and 24 units of free hydrochloric acid, respectively. Roentgenograms were entirely normal.

On June 20, 1938, the entire gastric mucosa was swollen and nodular. Two superficial ulcerations were visible. On July 11 the nodule formation was less marked. A section of the middle portion of the lesser curvature was depressed and thinned and presented two bluish blood vessels. On July 25 many nodes were still visible. Large portions of the body of the stomach were atrophic, thin and gray. The diagnosis of rapidly progressive hyperplastic atrophic gastritis was made. By August 1 no proliferative hyperplastic changes were visible. Extensive atrophic areas were present in the lesser curvature, in the anterior wall and in the lower portion of the greater curvature. The impression gained was of diffuse atrophy of inflammatory origin. Up to this time the patient had been treated simply with a high caloric, bland diet. After this examination he received ascorbic acid, 0.025 Gm. daily from August 1 to August 11 and 0.10 Gm. daily from August 11 to September 2. On August 10 the mucosa of the antrum looked fairly normal. The atrophic changes of the body were unaltered. One week later extensive atrophy of the gastric mucosa was again observed. On August 31 the mucosa of the antrum and posterior wall appeared edematous and contained collections of adherent mucus. The atrophic changes of the body were still present. Administration of ascorbic acid now was discontinued. From September 2 to 19 the patient received daily intramuscular injections of Lederle's liver extract in 1 cc. amounts until a total of 17 cc. was reached. On September 8 extensive atrophic gastritis was seen, and it was unchanged by September 16. At this point liver therapy was discontinued, and the patient next received 0.10 Gm. of nicotinic acid daily. By September 26 the picture had changed entirely. Unusually severe superficial gastritis was present. The mucosa was edematous and diffusely reddened, and there were extensive layers of adherent mucus. The atrophic areas were covered by this mucus, and it was considered that a superficial inflammation was superimposed on an atrophic mucosa. During the week preceding this examination the patient complained of increased weakness, so the administration of nicotinic acid was discontinued. On October 12 examination showed that the severe superficial gastritis had disappeared and only atrophy of the mucosa was present. On October 31 there was again extensive atrophic gastritis. The atrophic gastritis was more marked two weeks later, and vitamins in the form of "ABD capsules" were given twice daily. Unfortunately the patient was required to undergo a bilateral radical sinus operation, and for a time no gastroscopic examinations could be made. The administration of vitamins was discontinued from December 9 to 13 but was then resumed. On Feb. 1, 1939, a spectacular improvement was noted. The mucosa of the antrum appeared slightly thinner than normal, but the severe atrophic changes of the body of the stomach had disappeared almost completely. Only a small area, in the midportion of the lesser curvature, presented several extremely small gray patches containing red blood vessels. An examination on March 9 revealed recurrence of extensive atrophy despite the administration of vitamins in reduced doses.

This report is only preliminary. The case was of great interest, because we were able to witness the development and progression of

severe atrophic gastritis at regular and frequent gastrosopic examinations. Attempts to influence the atrophic gastritis by giving the patient liver extract, ascorbic acid and nicotinic acid were in vain. A spectacular improvement was noted during therapy with a mixture of vitamins. In this period of improvement, a radical nasal sinus operation was performed, but it seemed unlikely that the elimination of foci of infection could lead to the regeneration of atrophic gastric mucosa. It was possible that this improvement was coincidental, since the atrophy recurred while vitamin therapy was continued. However, the doses of vitamins, prior to the last gastrosopic examination had been reduced to one half the original amount. This patient is being observed carefully, and a more complete study will be reported later.

CASE 5—Spectacular improvement of atrophic gastritis following liver therapy and recurrence after discontinuation of treatment

A 64 year old German laborer was hospitalized on Aug 16, 1938, because of an old depressed skull fracture. He also had experienced, for several years, severe colicky pain in the upper part of the abdomen one or two hours after meals. The pain was relieved by vomiting. Treatment for ulcers at another institution had been ineffective. The physical examination gave negative results except to disclose a depression of the left frontal region of the skull.

A histamine test on August 21 with 0.75 mg. and on November 17 with 0.68 mg. showed complete anacidity. A third histamine test, on Jan 11, 1939, with 0.69 mg., revealed 10 units of free hydrochloric acid after forty minutes. No occult blood was found in the stools. Five blood counts were normal. Roentgenologic examination demonstrated a very small diaphragmatic herniation of the stomach. The esophagus, duodenum, colon and gallbladder were normal.

Six gastrosopic examinations were performed. After the second, intramuscular injections of 2 cc. of Lederle's liver extract were given for seventeen days (October 12 to 29), the patient receiving a total of 12 cc. A second course of liver therapy was administered between the fifth and sixth gastrosopic examinations, the patient receiving 1 cc. weekly (Jan 25 to March 8, 1939) until a total of 6 cc. was reached.

On Aug 29, 1938, gastrosopic examination showed that the pylorus and the antrum were normal. The mucosa of the anterior wall was thinned with a gray admixture. There was a protrusion of the posterior wall, covered with nodes and gray-whitish areas, which, however, became flatter by inflation of air. The mucosa of the posterior wall and the greater curvature above this protrusion was somewhat stiff and bumpy and presented grayish areas between the elevations. In the highest level the gastric mucosa was thinned and pinkish gray and contained many blood vessels. An impression of severe hyperplastic atrophic gastritis was gained. On October 12 some nodes were still seen but the prominence of the posterior wall had disappeared. Almost the entire body of the stomach was atrophic. The impression given was of extensive atrophic gastritis. On November 14 two definite gray spots on the anterior wall were the only remnants of the previously severe atrophic gastritis. This showed spectacular improvement of atrophic gastritis with liver therapy. On December 14 gastrosopic examination revealed a small area of atrophy above the angulus. On Jan 25, 1939, the mucosa of the antrum was slightly atrophic. The mucosa of the greater curvature and the posterior wall of the midportions of the stomach were so thin that blood vessels were visible. There

were fresh hemorrhages in the atrophic mucosa of the posterior wall. This showed that the atrophic gastritis had become worse again.

Spectacular improvement of extensive atrophic gastritis apparently followed the first course of liver therapy, although slight areas of atrophy still were visible. The original picture reappeared after discontinuation of the liver therapy. There was no improvement after the second course of such therapy, however, and further study is required to evaluate its effectiveness in this case. The case is of interest because of the appearance of free hydrochloric acid after liver therapy, suggesting, perhaps, a true regeneration of functionally active glandular structures in the stomach, even though this improvement was temporary.

CASE 6—Atrophic gastritis disappearing after liver therapy but reappearing after the discontinuation of this treatment

This case has been reported elsewhere and is therefore summarized briefly here. A 49 year old white American housewife had complained of rather generalized abdominal distress for twenty-five years. She suffered from marked fatigue and nervousness. The physical examination gave essentially negative results. She was observed from Jan 27, 1932, until June 24, 1936.

Gastric analysis after an Ewald test meal and three histamine tests, each with 0.5 mg, revealed no free hydrochloric acid. There was no occult blood in the stools. Frequent blood counts were normal. All roentgenologic examinations gave negative results. Four gastroscopic examinations were performed. After the second the patient received intramuscular injections of 1 cc of Lederle's liver extract until a total of 25 cc was given (April 13 to Sept 12, 1936).

Gastroscopic examination on July 12, 1935, revealed severe atrophic gastritis of the body of the stomach (diffuse thinning with visible red and blue blood vessels). On March 24, 1936, there was extensive atrophic hemorrhagic gastritis extending from the angulus to the cardia. Liver therapy was instituted after this examination. On June 15 in the midportion of the anterior wall there were two pinpoint hemorrhagic areas. Otherwise the gastric mucosa looked normal. Liver therapy was continued until September 12, when the patient voluntarily discontinued it. Examination on October 28 revealed patchy gray areas on the anterior and posterior wall, which were more extensive in the highest portions of the stomach. The changes, however, were less pronounced than those seen at the first gastroscopic examination.

This was our first case of marked atrophic gastritis in which an apparent improvement was observed following liver therapy. This, it seemed to us, was a remarkable therapeutic result, the significance of which was further emphasized by the reappearance of the typical gastroscopic signs of atrophic gastritis after the patient discontinued treatment.

CASE 7—Extensive atrophic gastritis with marked improvement following liver therapy

A 42 year old American saleswoman had had a diagnosis of psychoneurosis with secondary depression. The possible relation between her emotional problems and the atrophic gastritis will not be considered. She entered the hospital on July 11, 1938, because of intermittent dull aching pain in the epigastrium of ten years' duration and sharp epigastric pain of six weeks' duration occurring two hours after

meals This pain was relieved by food, usually milk, alkalis gave only temporary relief The physical examination gave negative results

Three histamine tests, each with 0.6 mg, indicated complete anacidity The stools contained no blood Three blood counts were normal Roentgenograms of the gastrointestinal tract also were normal Four gastroscopic examinations were performed Between the third and fourth the patient received, within one month (August 29 to September 22), 4 cc of Lederle's liver extract intramuscularly in divided doses

On July 14 the mucosa of the lower part of the posterior wall looked smooth but mottled, circular dark red mucosal hemorrhages were seen in this region Marked changes were seen in the midportions of the stomach the thin gray smooth mucosa contained fine red blood vessels Branching blue blood vessels were noted in the highest portions of the lesser curvature The impression of extensive atrophic hemorrhagic gastritis was received On August 5 there were extensive atrophic areas on the midportion and upper portion of the stomach Two weeks later scattered patches of mucus were present in the antrum One gray atrophic patch was observed in the angulus (i.e., much lower than the changes seen at the previous examination) The atrophic changes of the midportion and upper portion of the stomach were unaltered Liver extract was then administered, as mentioned previously On November 2 the picture had changed so much that it was hardly recognizable No atrophy and no blood vessels were seen The number of highlights was perhaps still slightly increased, but the atrophic changes, if still present, were amazingly reduced since the last examination

We have never before observed such spontaneous improvement of severe atrophic gastritis, although the senior author has observed several cases of severe involvement over a number of years Three gastroscopic examinations before institution of liver therapy showed no improvement in this case and serve therefore as control observations The sudden disappearance of the atrophy following the brief period of liver therapy suggests a specific therapeutic result

CASE 8—Marked improvement of atrophic gastritis following liver therapy

This case is reported very briefly because the gastroscopic observations were exceedingly difficult owing to a lack of cooperation on the part of the patient A 34 year old American housewife had received various forms of treatment, including liver therapy, for persistent anemia, no liver therapy, however, had been given since 1935 Her chief complaints were epigastric tenderness and weakness The physical examination gave essentially negative results

The hemoglobin content from Sept 11, 1933 to Feb 6, 1939, varied between 74 and 82 per cent and the red blood cell count between 3,700,000 and 4,810,000 A special hematologic examination showed no evidence of pernicious anemia Three histamine tests, with 0.3 mg and 0.4 mg, revealed 10 to 48 units of free hydrochloric acid Roentgenologic examinations gave negative results Gastroscopic examinations were performed on July 30, 1938, and Feb 6, 1939 Between these examinations the patient received a total of 16 cc of Lederle's liver extract intramuscularly

On July 23, 1938, gastroscopic examination revealed that the mucosa of the antrum was slightly gray Small grayish patches were seen in the anterior wall above the angulus These changes became more marked and larger toward the cardia, and large areas of smooth pinkish gray mucosa with small red blood vessels

and a few large blue blood vessels were seen in the fornix. A beanlike prominence (inflammatory polyp) was seen in the midportion of the lesser curvature. An impression of extensive atrophic gastritis of almost the entire stomach was gained. The liver therapy followed this examination. On Feb 6, 1939, gastroscopic examination showed that the antrum was normal. The atrophic changes had diminished markedly. The mucosa was still slightly thinned in the lower portions of the lesser curvature and the anterior wall.

A definite improvement of the atrophic gastritis in this case followed liver therapy. It should be noted here that anacidity is proved by histamine tests in only one third of all cases of atrophic gastritis. This case demonstrates that free hydrochloric acid may be present despite extensive atrophy of the gastric mucosa.

CASE 9—Apparent healing of atrophic gastritis following iron therapy in a case of hypochromic anemia

A 43 year old Jewish housewife was seen originally by her local physician in May 1938 because of marked fatigue, which in November 1938 bordered on exhaustion. She had been treated for anemia by injections of liver extract. She was first seen at Albert Merritt Billings Hospital on Dec 20, 1938, still complaining of marked fatigue.

An examination of the blood revealed a hemoglobin content of 35 per cent and a red cell count of 3,670,000. Study of a stained blood smear revealed moderate anisocytosis and a number of polychromatophilic cells. Gastric analysis after an Ewald test meal and two histamine tests, with 0.61 mg on Jan 3 and 0.64 mg on Feb 2, 1939, indicated complete anacidity. Roentgenologic studies gave normal results. Iron therapy (0.2 Gm of ferrous sulfate five times daily) was started immediately after the first gastroscopic examination, on Dec 30, 1938. The patient improved in a short time, although she continued to feel somewhat tired. The hemoglobin content rose to 80 per cent and the red blood cell count to 4,570,000.

Gastroscopic examination on Dec 30, 1938, revealed that the mucosa of the body of the stomach was markedly atrophic. Large areas were seen in which the mucosa appeared to be thin and gray and contained large nets of blood vessels. This gave an impression of extensive atrophic gastritis. It might be mentioned at this point that atrophy and pallor cannot be confused gastroscopically as each gives its own characteristic picture. The two are often observed together in pernicious anemia. On Feb 6, 1939, a tiny gray area containing a blood vessel was seen in the midportion of the stomach. All the other atrophic changes seen previously had disappeared, and the gastric mucosa appeared entirely normal. There was spectacular, almost complete, healing of the atrophic gastritis following iron therapy.

Apparent healing of atrophic gastritis following iron therapy has been described by Chevallier and Moutier² and by Schiff and Goodman⁴. This is the first case in which we have been able to make the same observation.

COMMENT

In evaluating the effectiveness of specific therapeutic measures, a thorough knowledge of the natural history of the disease is imperative. The senior author has observed a sufficient number of cases of untreated

atrophic gastritis to warrant the statement that severe atrophic gastritis does not completely disappear spontaneously. This impression is confirmed by the findings in case 1 and the control observations in cases 4, 5 and 6. Despite this previous experience, we feel that by studying the natural evolution of the disease in many more cases, the danger of attributing specific curative effects to perhaps only coincidental results, such as occurred in case 4, will be avoided.

It is obvious from this preliminary report that in many cases atrophic gastritis does not respond to specific substitution treatment. In other cases the improvement is temporary. Whether or not these results indicate causes of atrophic gastritis other than a deficiency state is chiefly speculative. On the other hand, the findings in cases 6 to 9 suggest a deficiency factor and, furthermore, justify the continued use of specific substitution therapy. The mechanism of the action of iron and liver in changing the appearance of the mucosa in iron deficiency anemia and pernicious anemia is as yet completely unknown.

SUMMARY

The effect of substitution therapy on the course of atrophic gastritis, as witnessed by gastrosopic examination in 8 cases, is described in a preliminary report.

Liver therapy was ineffective in case 2, and liver and iron therapy was ineffective in case 3. In case 4 the condition was unaffected by liver, ascorbic acid and nicotinic acid and probably by vitamins. In cases 5 to 8 the gastric mucosa became apparently normal after liver therapy. When this treatment was interrupted, the atrophy reappeared in 2 cases. Iron therapy was apparently successful in case 9.

It is impossible in the present state of knowledge to say whether or not the apparent regeneration of the gastric mucosa is genuine, i. e., due to the formation of new glands. Microscopic studies are necessary to solve this question.

The use of substitution therapy, such as the administration of liver, iron or vitamins, is justified in the treatment of atrophic gastritis as an approach to clarifying the nature and pathogenesis of this condition. It must be emphasized that control studies, prolonged observation and competent interpretation of findings are necessary before evaluation of such therapy is possible.

VITAMIN A DEFICIENCY IN DIABETES MELLITUS

J G BRAZER, M D

AND

A C CURTIS, M D

ANN ARBOR, MICH

The occurrence of increased amounts of carotene in the blood of patients with diabetes mellitus has long been recognized both by the clinical observation of xanthosis and by the results of laboratory tests. As early as 1904 von Noorden and Isaac¹ commented on the yellow pigmentation occurring in some patients with diabetes mellitus. In 1914 Palmer and Eckles² showed that carotene was present in the blood in the form of a carotoalbumin, and in 1919 Hess and Myers³ correlated the occurrence of increased amounts of carotene in the blood with the yellowish pigmentation of the skin previously noted by von Noorden. In 1929 and 1930 Rabinowitch⁴ noted that in patients with diabetes mellitus and xanthosis the diabetes appeared to be more severe and more difficult to control than in those without hypercarotenemia. In 85 per cent of 500 cases of diabetes mellitus studied at that time the carotene values were above normal. Later Rabinowitch⁵ stated that for some unknown reason patients with diabetes mellitus tend to retain vegetable pigments more than do patients without diabetes and that this accounts for the high incidence of hypercarotenemia among persons with diabetes.

From the Department of Internal Medicine, University of Michigan Medical School

1 von Noorden, C, and Isaac, S, 1904, cited in *Die Zuckerkrankheit und ihre Behandlung*, ed 8, Berlin, Julius Springer, 1927

2 Palmer, L S, and Eckles, C A. Carotin, the Principal Natural Yellow Pigment of Milk Fat, Its Relations to Plant Carotin and the Carotin of the Body Fat, Corpus Luteum and Blood Serum. I The Chemical and Physiological Relation of the Pigments of Milk Fat to the Carotin and Xanthophylls of Green Plants, *J Biol Chem* **17** 191, 1914

3 Hess, A J, and Myers, V C. A New Clinical Picture, *J A M A* **73** 1743 (Dec 6) 1919

4 Rabinowitch, I M. Cholesterol Content of Blood Plasma in Diabetes Mellitus and Juvenile Diabetes, *Arch Int Med* **43** 363 (March) 1929, Carotinemia and Diabetes, *ibid* **45** 586 (April) 1930

5 Rabinowitch, I M. Observations on Significance of Cholesterol Content of Blood Plasma in Diabetes Mellitus, *Canad M A J* **28** 162 (Feb) 1933

White and Gordon,⁶ using a modification of Palmer's⁷ method for determining the amount of carotene in the blood, studied the values for carotene in the blood of normal persons and of patients with diabetes mellitus and observed that the normal range was from 2 to 8 dichromate units. In patients with diabetes mellitus the values ranged from 5 to 25 dichromate units, averaging 14 units. Later studies by Stueck, Flaum and Ralli⁸ reported the average amount to be 26 dichromate units in patients with diabetes mellitus.

Drummond, Gilding and MacWalter⁹ injected carotene into the saphenous vein of cats and noted that it was rapidly absorbed by the reticuloendothelial system. The greatest concentration was in the Kupffer cells of the liver. A slight amount was found in the lungs and in the spleen.

Ralli, Brandaleone and Mandelbaum¹⁰ in 1935 and Ralli, Pariente and Brandaleone¹¹ in 1936 gave diets with the same carotene content to a group of patients with diabetes mellitus and to a group of normal persons. The patients with diabetes mellitus had higher initial blood carotene levels than did the normal group, and the content increased more rapidly with the high carotene diet and fell more slowly when that diet was discontinued than in the normal group. This study, coupled with determinations of the carotene content of the livers of diabetic patients who came to autopsy, led to a possible explanation of the high values of carotene in the blood of patients with diabetes mellitus. It was believed that this high value was a result of the inability of the livers to convert carotene to vitamin A, resulting in an accumulation of carotene in the blood stream. The cholesterol content of the blood of control persons averaged 173 mg per hundred cubic centimeters, and that of patients with diabetes mellitus, 203 mg per hundred cubic centimeters.

6 White, F. D., and Gordon, E. M. Estimation of Serum Carotene, *J. Lab. & Clin. Med.* **17** 53 (Oct.) 1931.

7 Palmer, L. S. Carotinoids and Related Pigments, New York, The Chemical Catalogue Company, 1922.

8 Stueck, G. H., Flaum, G., and Ralli, E. P. Serum Carotene in Diabetic Patients, with Clinical Evidence of Carotenemia as Determined by Photo-Electric Colorimeter, *J. A. M. A.* **109** 343 (July 31) 1937.

9 Drummond, J. C., Gilding, H. P., and MacWalter, R. J. Fate of Carotene Introduced into the Circulation, *J. Physiol.* **82** 75 (Aug.) 1934.

10 Ralli, E. P., Brandaleone, H., and Mandelbaum, T. Studies of the Effect of Administration of Carotene and Vitamin A in Diabetics, *J. Lab. & Clin. Med.* **20** 1266 (Sept.) 1935.

11 Ralli, E. P., Pariente, A. C., Brandaleone, H., and Davidson, S. Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus. Effect of Daily Administration of Carotene on the Blood Carotene of Normal and Diabetic Individuals, *J. A. M. A.* **106** 1975 (June 6) 1936.

Heymann¹² reported similar feeding experiments with a normal group and with a group of patients with diabetes mellitus. He also observed higher initial values of carotene in the blood of patients with diabetes mellitus than in that of the normal group. When equivalent amounts of carotene were fed to the two groups, the values for carotene increased more rapidly, reached higher levels and tended to remain elevated for a longer period of time after the diet was discontinued in the diabetic than in the normal group. It was felt that this was not due to the accompanying hypercholesterolemia or hyperglycemia.

Clausen¹³ in 1933 found that the vitamin A content of the liver of a patient with diabetes mellitus studied at autopsy was low. Jeghers¹⁴ in 1937, while studying various types of diseases, reported that the liver is the main storage depot of vitamin A and that it regulates the concentration of vitamin A throughout the body. Moore¹⁵ in 1937 observed that the reserves of vitamin A were above normal in the livers of patients with diabetes mellitus who had come to autopsy and suggested that the high level tends to rule out the theory that the liver of the diabetic person is unable to convert carotene to vitamin A. He stated the belief that both carotene and vitamin A accumulate in patients with diabetes mellitus because of a general slowing down of the metabolism of the body.

In 1938 Bessey and Wolbach¹⁶ postulated that the carotene content of the plasma is a measure of the difference between the rate of absorption from the intestines and the rate of conversion into vitamin A and also that the rate of conversion is diminished in patients with diabetes mellitus and with certain diseases of the liver.

The foregoing studies have suggested several explanations, which are somewhat at variance, for the relation between the amount of carotene and that of vitamin A in the blood of patients with diabetes mellitus. If one is to accept Ralli's¹¹ explanation that the increased amount of carotene, is due to an inability of the liver of a patient with diabetes mellitus to convert carotene to vitamin A, it would seem to follow that a state of vitamin A deficiency might well tend to develop in

12 Heymann, W. Carotenemia in Diabetes, *J A M A* **106** 2050 (June 13) 1936

13 Clausen, S. W. Limits of Anti-Infective Value of Pro-Vitamin A (Carotene), *J A M A* **101** 1384 (Oct 28) 1933

14 Jeghers, H. Night Blindness as Criteria of Vitamin A Deficiency. Review of Literature with Preliminary Observations of Degree of Vitamin A Deficiency Among Adults in Health and Disease, *Ann Int Med* **10** 1304 (March) 1937

15 Moore, T. Vitamin A and Carotene. Vitamin A Reserve of Adult Liver in Health and Disease, *J Biol Chem* **31** 155 (Jan) 1937

16 Bessey, O. A., and Wolbach, S. B. Vitamin A. Physiology and Pathology, *J A M A* **110** 2072 (June 18) 1938

such a patient in spite of an adequate intake of carotene. The proof of the occurrence of night blindness, clinical or subclinical, or other evidence of the presence of vitamin A deficiency in a group of patients with diabetes mellitus might well tend to substantiate this suggested paradox of vitamin A deficiency in the face of the high carotene content of the blood.

The biophotometric determination of early vitamin A deficiency suggested a means of studying this problem in patients with diabetes mellitus. Jeghers,¹⁴ using the biophotometer in a study of diseases of the liver, reported among his control groups 1 case of diabetes mellitus in which the biophotometer reading was below normal. Later Feldman¹⁷ tested a series of 8 patients with diabetes mellitus by means of the adaptometer and noted that 4 of the 8 showed evidence of dysadaptation.

With all these facts in mind the following study was undertaken.

METHOD

With a Froebel-Faybor biophotometer and according to the methods outlined by Jeans, Blanchard and Zentmire¹⁸ and by Jeghers,¹⁹ a series of 20 interns and staff members of the University Hospital were tested by the same observer under like conditions, and the results were tabulated and checked. Readings in the experiments were recorded in milli-foot-candles instead of as direct biophotometer readings. In each case readings were made at the following times: (1) on entering the dark room, (2) after a ten minute period in the dark, (3) twenty seconds after a three minute period of bleaching, (4) after three minutes of recovery, (5) after six minutes of recovery and, finally, (6) after ten minutes of recovery.

All members of the control group ate a diet which had a minimum vitamin A content of 4,000 U. S. P. units per day. The average biophotometric curve for the group was determined and compared with Jegher's¹⁹ "low normal" curve. The cholesterol content of the blood was determined in each instance by Sackett's²⁰ modification of Bloor's²¹ method. The carotene content was determined by White and Gordon's⁶ modification of Palmer's⁷ method and expressed as dichromate units.

17. Feldman, J. B. *The Use of the Photometer in Detecting Latent Avitaminosis A in Nutrition*. The Newer Diagnostic Methods. New York: The Milbank Memorial Fund, 1938.

18. Jeans, P. C., Blanchard, E. and Zentmire, Z. Dark Adaption and Vitamin A. A New Photometric Technic, *J. A. M. A.* **108** 451 (Feb. 6) 1937.

19. Jeghers, H. Degree and Prevalence of Vitamin A Deficiency in Adults with a Note on Its Experimental Production in Human Beings, *ibid.* **109** 756 (Sept. 4) 1937.

20. Sackett, G. E. Modification of Bloor's Method for the Determination of Cholesterol in Whole Blood or Blood Serum. *J. Biol. Chem.* **64** 203 (May) 1925.

21. Bloor, W. R., and Knudson, A. The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood. *ibid.* **27** 107 (Oct.) 1916.

A series of ambulatory young and early middle-aged patients, presenting either the classic history and clinical picture of diabetes mellitus or the definitely abnormal dextrose tolerance curves of the diabetic type, or both, were studied. All these patients had a type of diabetes which occurs in youth or in early middle life and is commonly called the juvenile type of diabetes mellitus. Each member of the group was studied in a manner similar to that employed for the control group. In addition, each was observed clinically for evidence of cutaneous changes suggestive of vitamin A deficiency and questioned regarding subjective evidence of night blindness.

All patients had their diabetes either controlled or in the process of being controlled during the study. Some showed glycosuria, but none had any clinical or laboratory signs of acidosis. All patients had ophthalmoscopic examinations by a competent ophthalmologist, and only those with normal fundi are reported on here. All biophotometric readings were made two hours postprandially.

A group of 7 patients with diabetes mellitus with subnormal biophotometer readings was given a daily supplement of 8 cc of carotene in vegetable oil,²² containing 60,000 U S P units of vitamin A, in divided doses for periods of seven days. Two patients in this group received the daily supplement for a period of fourteen days. In both groups biophotometric readings and determinations of cholesterol and carotene in the blood were obtained before and after the periods of supplementary feeding.

Twenty patients with diabetes mellitus were given a concentrated fish liver oil,²³ containing approximately 60,000 U S P units of vitamin A, as a daily supplement for periods ranging from three to twenty-one days. Biophotometer readings and blood cholesterol and blood carotene values were determined before and after the periods of supplementary feeding, and the results were tabulated and charted.

In order to show that the results were not coincidental, associated with "learning" or due to improvement in the diabetic status, the routine was varied in two ways: (1) by feeding the vitamin A supplement before the carotene supplement in a portion of the cases and (2) by depriving the group of the vitamin A supplement that had previously maintained normal or near normal biophotometer readings and then retesting them after short periods without the supplement.

RESULTS

The numerical readings for the control group shown in table 1 are expressed graphically in figure 1. It is to be noted that the reading twenty seconds after the bleaching exceeded the twenty second value reported by Jegheis,¹⁹ 0.74 milli-foot-candle, and the one reported by Colette, Youmans, Frank and Corlette,²⁴ 0.7 milli-foot-candle, in 10 cases but in no instance did it exceed the low borderline reading of

22 Smaco carotene in vegetable oil (1 cc contains 7,500 U S P units of vitamin A)

23 Parke, Davis haliver oil capsules, 'Natola' (1 capsule contains approximately 9,800 U S P units of vitamin A)

24 Corlette, M. B., Youmans, J. B., Frank, H., and Corlette, M. G. Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults, *Am J M Sc* **195** 54 (Jan) 1938

1 milli-foot-candle given by Jeans, Blanchard and Zentmire¹⁸ The readings after three, six and ten minutes of recovery were all well within the normal recovery range as advocated by Jegheis¹⁴ An average of the twenty sets of readings was established as the average normal reading for our biophotometer under the given conditions The blood carotene values for normal persons (table 1) ran higher than the previously reported observations, possibly because the subjects tested had slightly more than an adequate amount of carotene in the diet The average cholesterol value, of 200 mg per hundred cubic centimeters (table 1), agreed fairly well with what is generally considered the upper normal limit

A study of table 2 reveals the fact that all the readings taken after twenty seconds of recovery were lower than the lowest limit of borderline normal readings noted by Jeans, Blanchard and Zentmire,¹⁸ and all were much lower than any of those for the control subjects None of the twenty sets of readings in the periods three and six minutes after bleaching equaled those of the control group, and the values for only 3 of the 20 patients (1, 8 and 16) fell into the range between our normal average and Jegheis'¹⁹ low normal value (table 1) Three patients (5, 11 and 15) presented values within normal limits in one of the periods but not in both The carotene values, as expected, were higher than normal in 90 per cent of the cases studied (table 2), averaging 23 dichromate units, in contrast to an average of 13 dichromate units for the control group Of the 2 patients having low carotene values (5 and 18), 1 was markedly emaciated on admission, and the factor of low intake of carotene might have played a role in the determination The other patient had been on a low fat diet for a considerable time before the experiment Cholesterol values varied widely, from 154 to 342 mg per hundred cubic centimeters of blood, but the average was approximately 39 mg greater in the patients with diabetes The scatter graph (fig 2) graphically portrays the difference between the individual and the average readings for the diabetic patients and our average normal readings

Clinically, of 20 patients studied in table 2, 3 gave a history of night blindness and 9 showed keratosis pilaris, which is described as one of the manifestations of vitamin A deficiency¹⁶

A group of 7 patients with diabetes mellitus was given crystalline carotene dissolved in vegetable oil, 60,000 U S P units of vitamin A, daily for seven days Table 3 shows that there was relatively little change in the readings before and after the supplement Slight improvement was noted in the reading after twenty seconds of recovery for patients 2, 3 and 6, but in no case did the readings approach normal

TABLE 1—*Biophotometer Readings for Twenty Supposedly Normal Males, with the Simultaneously Determined Values of Carotene and Cholesterol in the Blood*

Patient	Initial Reading in Dark Room, Milli Foot Candles	After 10 Minute Dark Period Milli Foot Candles	Light	20 Seconds After 3 Minute Bleach Milli Foot Candles	3 Minute Recovery Milli Foot Candles	6 Minute Recovery Milli Foot Candles	10 Minute Recovery Milli Foot Candles	Blood Carotene Dichromate Units	Blood Cholesterol Mg per 100 Cc
1	0.18	0.01		1.00	0.11	0.03	0.01	17	276
2	0.92	0.18		0.63	0.08	0.03	0.01	14	
3	0.24	0.10		0.26	0.10	0.03	0.04	12	203
4	0.63	0.12		0.41	0.03	0.03	0.05	12	194
5	0.69	0.14		0.58	0.16	0.05	0.02	15	248
6	0.76	0.11		0.84	0.15	0.09	0.02		186
7	0.58	0.06		0.92	0.14	0.06	0.03	10	205
8	0.92	0.08		0.58	0.15	0.09	0.02	12	183
9	0.47	0.05		0.92	0.14	0.06	0.05	16	177
10	0.58	0.14		0.76	0.14	0.07	0.03	15	230
11	0.24	0.02		0.53	0.11	0.05	0.02	14	202
12	0.63	0.05		0.69	0.15	0.03	0.03	14	192
13	0.84	0.04		0.92	0.19	0.06	0.03	12	182
14	0.84	0.04		0.63	0.11	0.06	0.03	16	178
15	0.47	0.03		1.00	0.22	0.05	0.03	14	233
16	0.63	0.07		0.92	0.16	0.06	0.02	14	206
17	0.47	0.05		0.84	0.16	0.05	0.03	14	156
18	0.84	0.10		0.84	0.26	0.12	0.05	12	147
19	0.63	0.07		0.92	0.22	0.11	0.04	14	222
20	0.58	0.03		0.69	0.16	0.04	0.02	12	176
Average normal	0.61	0.07		0.75	0.15	0.07	0.03	13	200
Jegher's low normal	0.80	0.28		0.74	0.32	0.14	0.10		

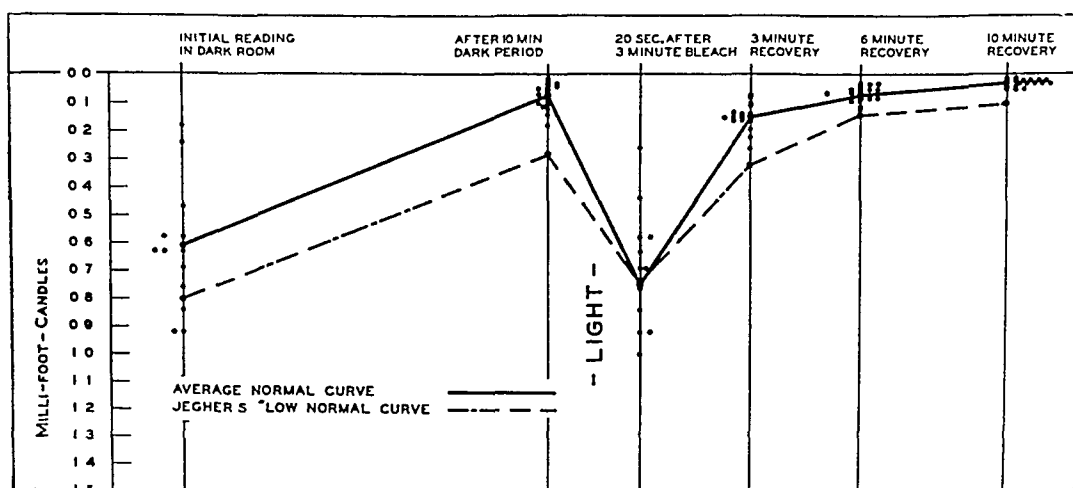


Fig 1—Frequency distribution of determinations on normal males (table 1)
The average normal curve is compared with Jegher's low normal curve

figures. The conditions in the remainder of the patients were unchanged or became worse while they received the carotene supplement during the seven and fourteen day periods. Normal readings after three and six minutes of recovery were noted in 1 instance (patient 2), and slight improvement was noted in patient 3. The remaining 5 patients showed

TABLE 2—Biophotometer Readings for Twenty Persons with Juvenile Diabetes (with Normal Fundi), Compared with the Readings for Normal Males (Table 1)

Patient	Initial Reading in Dark Room, Mill Foot Candles	After 10 Minute Dark Period, Mill Foot Candles	Light	20 Seconds After 3 Minute Bleach, Mill Foot Candles	3 Minute Recovery, Mill Foot Candles	6 Minute Recovery, Mill Foot Candles	10 Minute Recovery, Mill Foot Candles	Blood Carotene Diebromite Units	Blood Cholesterol Mg per 100 Cc
1	1.36	0.03		1.92	0.26	0.06	0.02	30	342
2	0.92	0.14		1.80	0.35	0.19	0.08	24	250
3	1.22	0.18		2.40	0.76	0.35	0.14	28	210
4	0.84	0.22		1.80	0.35	0.18	0.11	16	165
5	0.44	0.03		1.95	0.44	0.03	0.01	10	250
6	1.36	0.06		1.95	0.47	0.18	0.03	20	216
7	0.58	0.02		1.60	0.38	0.15	0.04	20	229
8	0.35	0.10		1.80	0.29	0.08	0.04	26	198
9	1.00	0.32		1.22	0.38	0.16	0.08	20	260
10	0.69	0.11		1.48	0.38	0.18	0.07		250
11	1.22	0.16		1.22	0.35	0.07	0.04	20	330
12	1.95	0.26		1.95	0.84	0.38	0.18	16	176
13	2.40	1.10		2.40	0.69	0.22	0.08	14	154
14	1.22	0.14		1.48	0.52	0.22	0.07	25	230
15	1.60	0.03		1.95	0.35	0.12	0.03	35	236
16	1.48	0.08		1.10	0.26	0.08	0.02	40	
17	0.44	0.06		2.16	0.44	0.18	0.01	18	306
18	0.76	0.29		2.40	0.38	0.19	0.11	8	283
19	1.10	0.22		2.40	0.84	0.52	0.26	40	234
20	0.92	0.29		1.95	0.84	0.47	0.24	28	220
Average reading	1.05	0.19		1.80	0.48	0.20	0.09	23	239
Normal	0.61	0.07		0.75	0.15	0.07	0.03	13	200
Difference	+0.44	+0.12		+1.05	+0.33	+0.13	+0.06	+10	+39

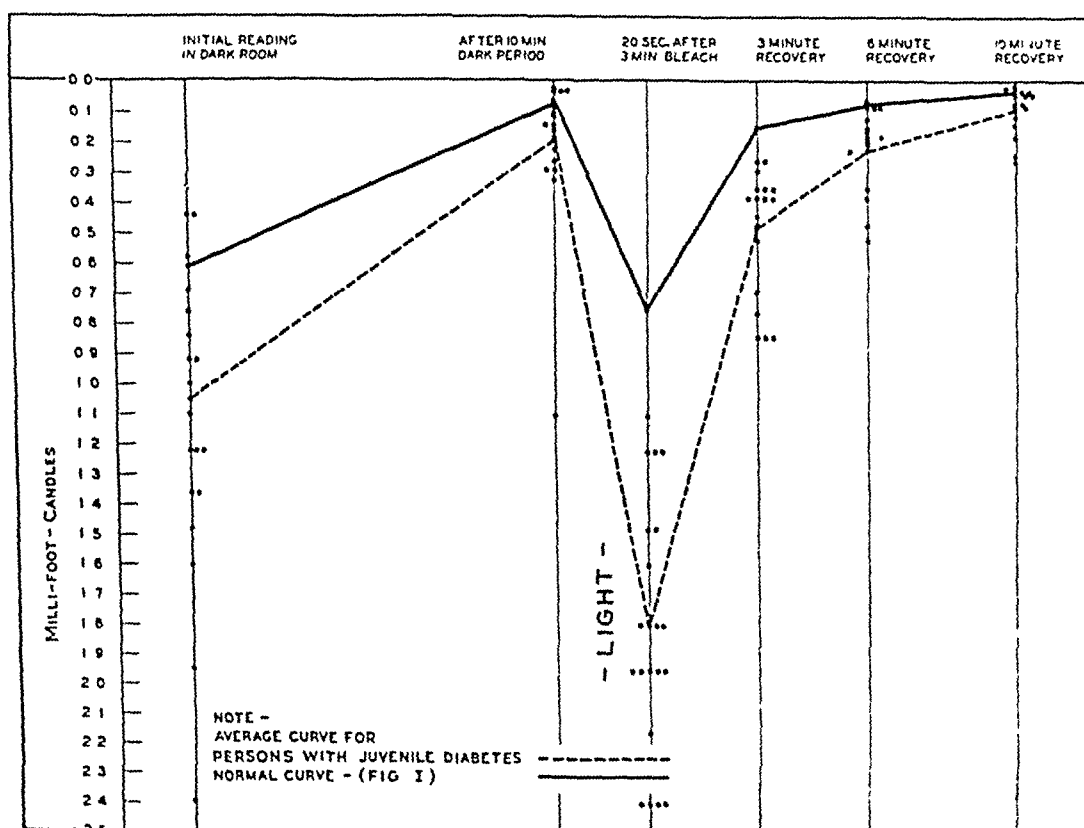


Fig 2—Frequency distribution of determinations on persons with juvenile diabetes (table 2) Compare the composite curve with the normal curve (fig 1)

TABLE 3—*The Effect on the Biophotometer Readings of Feeding Persons with Juvenile Diabetes 8 Cc of Carotene in Oil (Approximately 60,000 U S P Units of Vitamin A) per Day as a Supplementary Feeding*

Patient	8 Cc Carotene in Oil Daily	Initial Reading in Dark Room, Milli Foot Candles	After 10 Minute Dark Period, Milli Foot Candles	Light	20 Seconds After Minute Bleach, Milli Foot Candles	3 Minute Recovery, Milli Foot Candles	6 Minute Recovery, Milli Foot Candles	10 Minute Recovery, Milli Foot Candles	Blood Carotene Dichromate Units	Blood Cholesterol Mg per 100 Cc
1 A	Before carotene supplement	0.92	0.14		1.80	0.35	0.19	0.08	24	250
B	After carotene 7 days	1.48	0.26		1.80	0.58	0.26	0.14	26	208
2 A	Before carotene supplement	0.44	0.03		1.97	0.44	0.06	0.01	10	250
B	After carotene 7 days	0.32	0.02		1.22	0.24	0.03	0.02	30	236
3 A	Before carotene supplement	1.10	0.22		2.40	0.84	0.52	0.26	40	234
B	After carotene 7 days	1.60	0.19		1.48	0.32	0.19	0.11	40	192
4 A	Before carotene supplement	0.69	0.11		1.48	0.38	0.18	0.07		250
B	After carotene 7 days	1.60	0.19		1.95	0.63	0.26	0.08	30	210
5 A	Before carotene supplement	1.22	0.14		1.48	0.52	0.22	0.07	25	230
B	After carotene 7 days	1.22	0.23		2.16	0.58	0.22	0.14	35	172
6 A	Before carotene supplement	0.84	0.12		1.95	0.47	0.19	0.07	24	240
B	After carotene 7 days	1.22	0.09		1.60	0.44	0.16	0.06	25	194
C	After carotene 14 days	1.36	0.12		2.40	0.34	0.29	0.10	35	250
7 A	Before carotene supplement	2.40	0.06		2.40	0.76	0.22	0.08	25	212
B	After carotene 7 days	2.40	0.06		2.40	0.69	0.26	0.10	40	208
C	After carotene 14 days	2.40	0.19		2.40	0.69	0.32	0.11	50	220
Average for diabetic patients										
Before supplement		1.09	0.12		1.93	0.54	0.23	0.09	25	238
After 7 day supplement		1.41	0.15		1.80	0.54	0.20	0.09	32	203
Difference		+0.32	+0.03		-0.13	0	-0.03	0	+7	-35

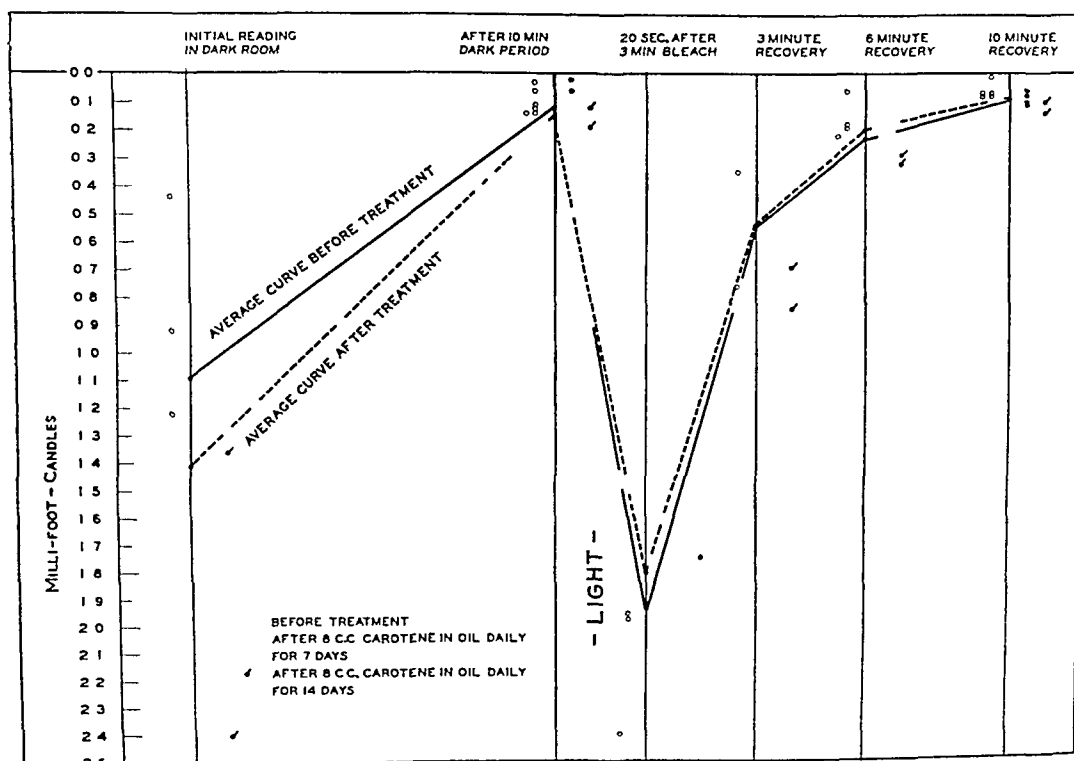


Fig 3—Frequency distribution of biophotometer readings for persons with juvenile diabetes before and after treatment with 8 cc of carotene in oil daily (table 3)

TABLE 4—*Biophotometer Readings for Persons with Juvenile Diabetes Before and After Feeding 12 Cc of Halibut Liver Oil Supplement (Approximately 60,000 U S P Units of Vitamin A) per Day for Varying Numbers of Days*

Patient	12 Cc Halibut Liver Oil Daily	Initial Reading in Dark Room, Milli Foot Candles	After 10 Minute Dark Period, Milli Foot Candles	Light	20 Seconds After 3 Minute Bleach, Milli Foot Candles	3 Minute Recovery Milli Foot Candles	6 Minute Recovery Milli Foot Candles	10 Minute Recovery Milli Foot Candles	Blood Carotene Dichromate Units	Blood Cholesterol Mg per 100 Cc
1	Before supplement	1.60	0.03		1.95	0.35	0.12	0.03	35	236
	After 3 days vitamin A	0.84	0.05		1.10	0.35	0.07	0.06	35	292
	Difference	-0.76	+0.02		-0.85	0	-0.05	+0.03	0	-26
2	Before supplement	0.92	0.03		1.10	0.35	0.16	0.04	24	260
	After 4 days vitamin A	0.76	0.04		1.00	0.24	0.10	0.03	22	292
3	Before supplement	0.92	0.10		1.48	0.35	0.14	0.07	30	271
	After 4 days vitamin A	1.00	0.09		0.76	0.22	0.11	0.05	30	244
4	Before supplement	1.00	0.14		1.10	0.35	0.19	0.09	40	192
	After 4 days vitamin A	1.36	0.03		0.52	0.16	0.07	0.04	40	220
	Average before supplement	0.95	0.09		1.23	0.35	0.16	0.07	31	242
	Average after 4 days vitamin A	1.04	0.06		0.76	0.21	0.09	0.04	31	232
	Difference	+0.09	-0.03		-0.47	-0.14	-0.07	-0.03	0	-10
5	Before supplement	0.92	0.16		1.36	0.29	0.09	0.05	24	222
	After 5 days vitamin A	0.38	0.03		0.92	0.14	0.08	0.02	30	212
6	Before supplement	0.44	0.02		1.60	0.14	0.05	0.03	30	216
	After 5 days vitamin A	0.35	0.02		0.58	0.03	0.02	0.01	30	216
	Average before supplement	0.68	0.09		1.48	0.22	0.07	0.04	27	219
	Average after 5 days vitamin A	0.36	0.03		0.80	0.09	0.05	0.01	30	214
	Difference	-0.32	-0.04		-0.68	-0.13	-0.02	-0.03	+3	-5
7	Before supplement	1.48	0.08		1.10	0.26	0.08	0.02	40	
	After 6 days vitamin A	1.10	0.16		0.76	0.26	0.15	0.02	40	
8	Before supplement	0.41	0.06		2.16	0.44	0.18	0.04	18	306
	After 6 days vitamin A	0.58	0.12		0.76	0.08	0.03	0.02	20	230
	Average before supplement	0.96	0.07		1.63	0.35	0.13	0.03	29	
	Average after 6 days vitamin A	0.87	0.14		0.76	0.17	0.09	0.02	30	
	Difference	-0.13	+0.07		-0.87	-0.18	-0.04	-0.01	+1	
9	Before supplement	1.22	0.16		1.22	0.35	0.08	0.04	20	330
	After 7 days vitamin A	0.63	0.18		0.52	0.24	0.11	0.08	24	234
10	Before supplement	1.00	0.32		1.22	0.38	0.16	0.08	20	260
	After 7 days vitamin A	0.76	0.47		1.48	0.38	0.14	0.11	18	210
11	Before supplement	0.58	0.02		1.60	0.38	0.15	0.04	20	229
	After 7 days vitamin A	0.92	0.09		0.63	0.09	0.04	0.02	25	203
12	Before supplement	1.60	0.29		1.60	0.58	0.29	0.12	20	250
	After 7 days vitamin A	1.22	0.09		1.00	0.32	0.18	0.11	25	234
13	Before supplement	0.92	0.10		1.80	0.47	0.19	0.08	24	216
	After 7 days vitamin A	0.76	0.08		1.36	0.38	0.19	0.08	25	234
	Average before supplement	1.06	0.18		1.49	0.43	0.17	0.07	23	257
	Average after 7 days vitamin A	0.86	0.18		1.00	0.28	0.17	0.05	23	267
	Difference	-0.20	0		-0.49	-0.15	-0.04	-0.02	-0	6
	Average before supplement	1.00	0.12		1.48	0.36	0.14	0.06	26	248
	Average after 37 days vitamin A	0.90	0.12		0.88	0.22	0.10	0.05	28	247
	Difference	-0.10	0		-0.60	-0.14	-0.04	-0.01	-2	-5
14	Before supplement	2.40	0.47		1.80	0.63	0.24	0.12	26	208
	After 8 days vitamin A	1.36			1.22	0.35	0.24		24	277
15	Before supplement	0.76	0.29		2.40	0.38	0.19	0.11	8	283
	After 8 days vitamin A	1.36	0.16		0.92	0.19	0.12	0.03	13	252
	Average before supplement	1.58	0.38		2.10	0.51	0.22	0.11	17	245
	Average after 8 days vitamin A	1.36			1.07	0.27	0.18		18	255
	Difference	-0.22			-1.03	-0.24	-0.04		-1	-10
16	Before supplement	2.16	0.26		2.16	0.52	0.22	0.18	28	188
	After 14 days vitamin A	0.84	0.03		1.00	0.24	0.16	0.05	24	148

TABLE 4—*Biophotometer Readings for Persons with Juvenile Diabetes Before and After Feeding 12 Cc of Halibut Liver Oil Supplement (Approximately 60,000 U S P Units of Vitamin A) per Day for Varying Numbers of Days—Continued*

Patient	12 Cc Halibut Liver Oil Daily	Initial Reading in Dark Room, Mill Foot Candles		20 Seconds After 3 Minute Bleach Mill-Foot Candles	3 Minute Recovery Mill Foot Candles	6 Minute Recovery, Mill Foot Candles	10 Minute Recovery Mill Foot Candles	Blood Carotene Dichromate Units	Blood Cholesterol Mg per 100 Cc
		After 10 Minute Dark Period, Mill Foot Candles	Light						
17	Before supplement	1 95	0 32	2 16	0 92	0 38	0 18	16	176
	After 14 days vitamin A	0 58	0 09	0 44	0 16	0 05	0 01	18	214
	Average before supplement	2 06	0 29	2 16	0 72	0 35	0 18	22	181
	Average after 14 days vitamin A	0 71	0 09	0 72	0 20	0 11	0 03	21	181
	Difference	-1 35	-0 20	-1 44	-0 52	-0 44	-0 15	-1	0
18	Before supplement	0 63	0 08	1 22	0 32	0 08	0 03	20	256
	After 15 days vitamin A	0 92	0 07	0 63	0 11	0 05	0 02	20	274
	Difference	+0 29	-0 01	-0 59	-0 21	-0 03	-0 01	0	+18
19	Before supplement	2 16	0 26	2 40	1 36	0 69	0 12	15	166
	After 15 days vitamin A	0 92	0 08	1 10	0 22	0 07	0 02	12	154
	Difference	-1 24	-0 18	-1 30	-1 14	-0 62	-0 10	-3	-12
20	Before supplement	0 84	0 15	1 60	0 38	0 29	0 06	22	214
	After 21 days vitamin A	1 48	0 44	1 95	0 58	0 19	0 09	24	228
	Difference	+0 64	+0 29	+0 35	+0 20	-0 10	+0 03	+2	+14
	Average before supplement	1 56	0 26	1 96	0 64	0 31	0 11	19	213
	Average after 8 21 days vitamin A	1 07	0 16	1 04	0 26	0 13	0 05	19	219
	Difference	-0 49	-0 13	-0 92	-0 38	-0 18	-0 06	0	+5
Grand average									
	Before supplement	1 20	0 17	1 65	0 46	0 21	0 08	25	236
	After 3-21 days vitamin A	0 91	0 13	0 93	0 24	0 11	0 05	25	235
	Difference	-0 29	-0 04	-0 72	-0 22	-0 10	-0 03	0	-1

no significant improvement, and the average for the group after carotene supplements were added to the diet showed little change from that before the giving of the supplements. An increase in the carotene content of the blood was noted for 5 of the 7 patients. Patient 3 had a high value throughout the study. The general trend of the cholesterol values after the addition of a carotene supplement to the diet was slightly downward but not consistently so. Figure 3 graphically portrays the lack of beneficial effect of feeding the carotene supplements.

Table 4 shows that of the 13 patients who received 60,000 U S P units of vitamin A daily in the form of fish liver oil for intervals of three to seven days, 12 showed improvement in the reading taken twenty seconds after bleaching. Of these 12, 7 had normal values (0.75 milli-foot-candle or less) and 4 close to normal (1 to 0.75 milli-foot-candle), and 1 had a slightly improved value. The thirteenth patient, no. 10, showed a slightly lower reading after the carotene supplement than before. Three and six minutes after recovery significant improvement was noted in 11 of the 13 patients, with slight improvement in the

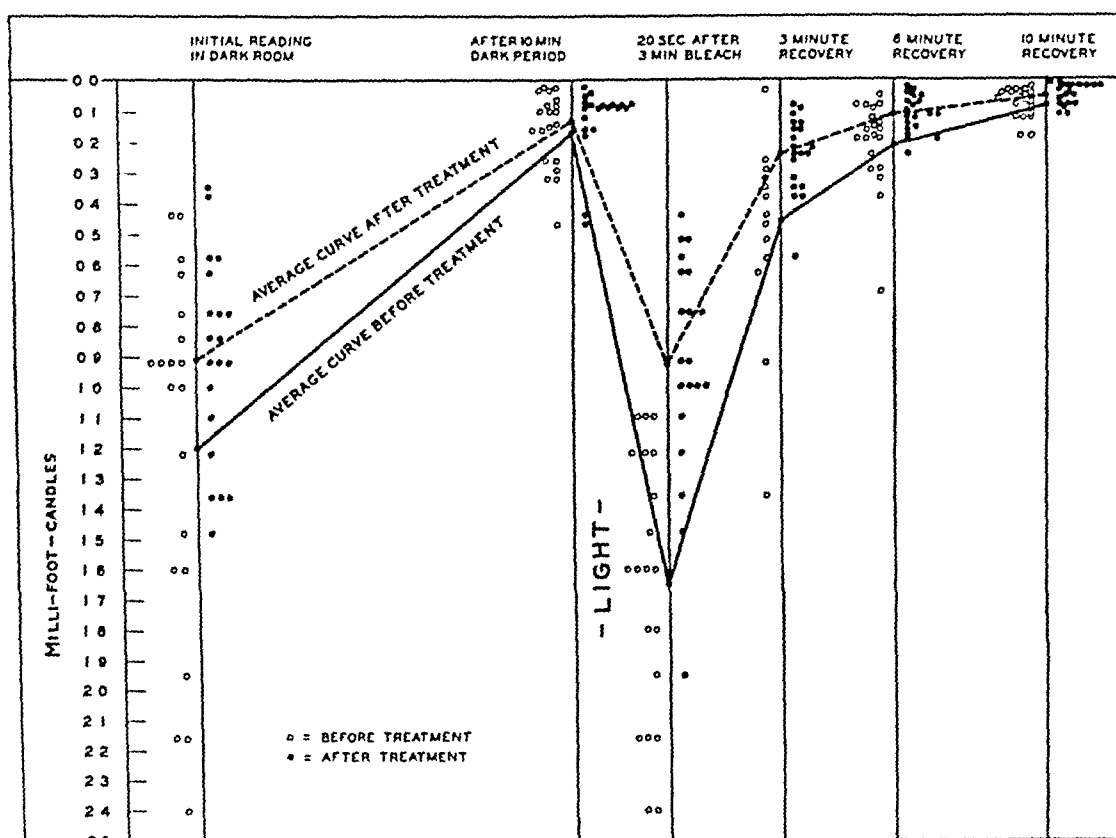


Fig 4—Frequency distribution of biophotometer readings for diabetic young persons before and after treatment with halibut liver oil supplement equivalent to 60,000 U S P units of vitamin A daily

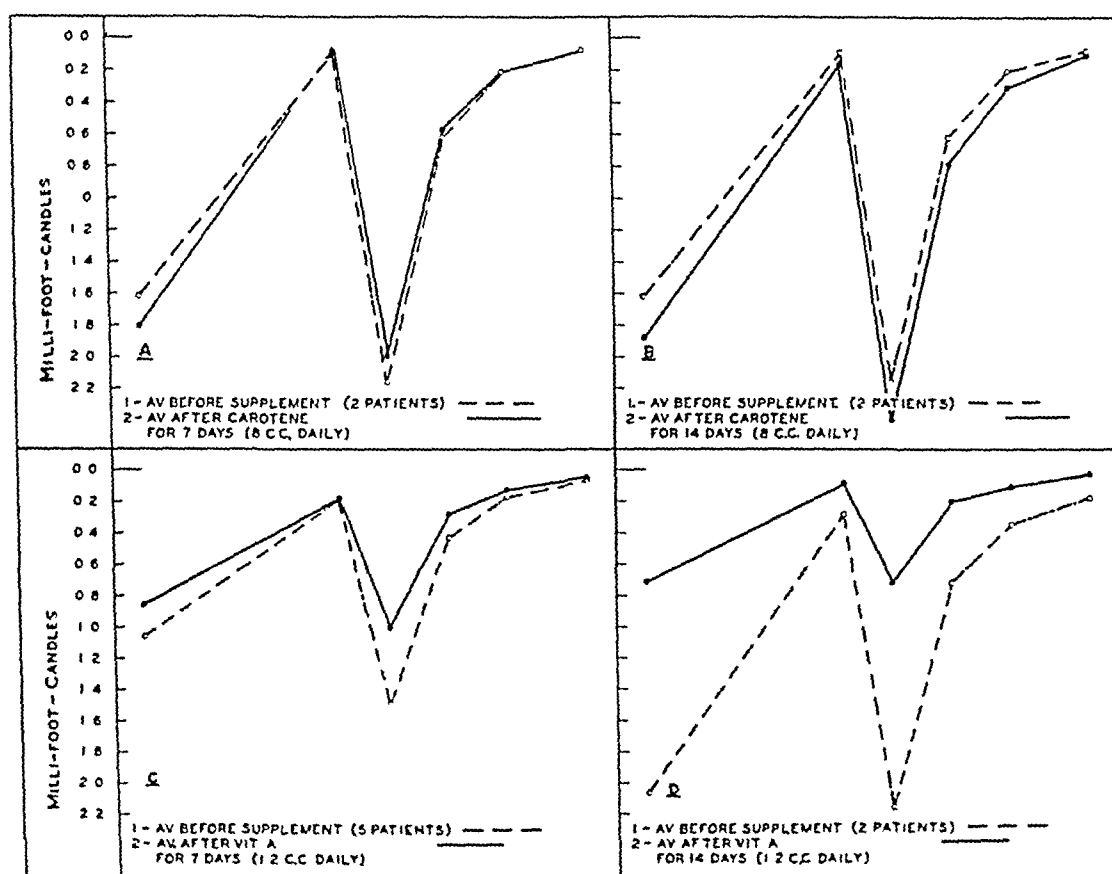


Fig 5—Comparison of the effect of carotene and vitamin A administered for periods of seven and fourteen days

remaining 20. In the patients that received vitamin A for eight to twenty-one days the results were similar to those obtained with the shorter period of administration.

Figure 4 graphically depicts the changes, including average curves before and after the fish oil supplement. There was relatively little change in the carotene and cholesterol values during this phase of the experiment. That there was no difference in the resultant effects of

TABLE 5—*The Effect of Removing Vitamin A Supplement from Diabetic Patients Whose Biophotometer Readings Had Been Previously Maintained at Normal or Slightly Subnormal Levels by the Vitamin A Supplement*

60,000 U S P Units of Vitamin A Daily			Initial Reading in Dark Room, Milli Foot Candles	After 10 Minute Dark Period, Milli-Foot Candles	Light	20 Seconds After 1 Minute Bleach Milli-Foot Candles	3 Minute Recovery, Milli Foot Candles	6 Minute Recovery Milli Foot Candles	10 Minute Recovery, Milli Foot Candles	Blood Carotene Dichromate Units	Blood Cholesterol Mg per 100 Cc
Patient											
1	A	For 4 days	1 00	0 09		0 76	0 22	0 11	0 05	30	244
	B	None for 5 days	0 84	0 12		1 22	0 28	0 14	0 09	25	236
2	A	For 5 days	0 35	0 02		0 58	0 03	0 02	0 01	30	212
	B	None for 6 days	0 84	0 12		1 95	0 47	0 19	0 07	24	240
3	A	For 7 days	0 92	0 09		0 63	0 09	0 04	0 02	25	203
	B	None for 6 days	0 84	0 03		0 92	0 19	0 08	0 03	30	234
4	A	For 34 days	0 84	0 09		1 00	0 24	0 16	0 05	22	148
	B	None for 7 days	2 40	0 38		2 40	0 76	0 22	0 08	25	212
5	A	For 5 days	0 35	0 02		0 58	0 03	0 02	0 01	30	216
	B	None for 12 days	0 32	0 02		1 00	0 08	0 04	0 02	30	180
6	A	For 7 days	0 76	0 08		1 36	0 38	0 19	0 08	25	234
	B	None for 14 days	1 10	0 14		1 95	0 52	0 18	0 08	16	156
7	A	For 4 days	1 36	0 05		0 52	0 16	0 07	0 04	40	220
	B	None for 20 days	1 00	0 08		1 48	0 29	0 12	0 04	40	176
8	A	For 30 days	1 10	0 11		0 92	0 24	0 11	0 06	12	154
	B	None for 20 days	1 80	0 14		1 95	0 52	0 19	0 05	10	221
9	A	For 6 days	0 58	0 12		0 76	0 08	0 03	0 02	40	
	B	None for 24 days	1 48	0 32		1 95	0 63	0 26	0 03	30	
10	A	For 14 days	0 58	0 09		0 38	0 16	0 05	0 01	18	214
	B	None for 35 days	2 16	0 29		1 22	0 32	0 08	0 06	20	197
11	A	For 15 days	0 92	0 70		0 63	0 11	0 05	0 02	20	274
	B	None for 5 months	2 40	0 76		2 40	0 92	0 58	0 44	28	258
	Average with supplement		0 80	0 08		0 74	0 16	0 08	0 03	27	212
	Average with no supplement		1 38	0 22		1 68	0 45	0 19	0 09	25	211
	Difference		+0 58	+0 14		+0 94	+0 29	+0 11	+0 06	-2	-1

administering the supplements over periods of fourteen days rather than seven days is shown graphically by figure 5, there was improvement with supplements of vitamin A but not with carotene.

The effect of removing vitamin A supplements from patients with diabetes mellitus whose biophotometer readings had previously been maintained at normal or nearly normal levels by means of the supplements is shown in table 5. After twenty seconds of recovery in 9 of the 11 cases the values became significantly abnormal after discontinuance of the supplements and in the remaining 2 cases they showed

drops to the borderline level. After three and six minutes of recovery the values in 6 of the 11 cases dropped to markedly abnormal levels after discontinuance of the supplements, and the values in the remaining 5 cases dropped to lower but not abnormal levels. The result certainly seems to show that the previously noted improvement while the patients were receiving vitamin A supplements was due to the supplements themselves and not to coincidence or "learning" factors. Figure 6 graphically depicts these changes, with average curves before and after the use of the supplements was discontinued. No significant changes were noted in the values for cholesterol or carotene.

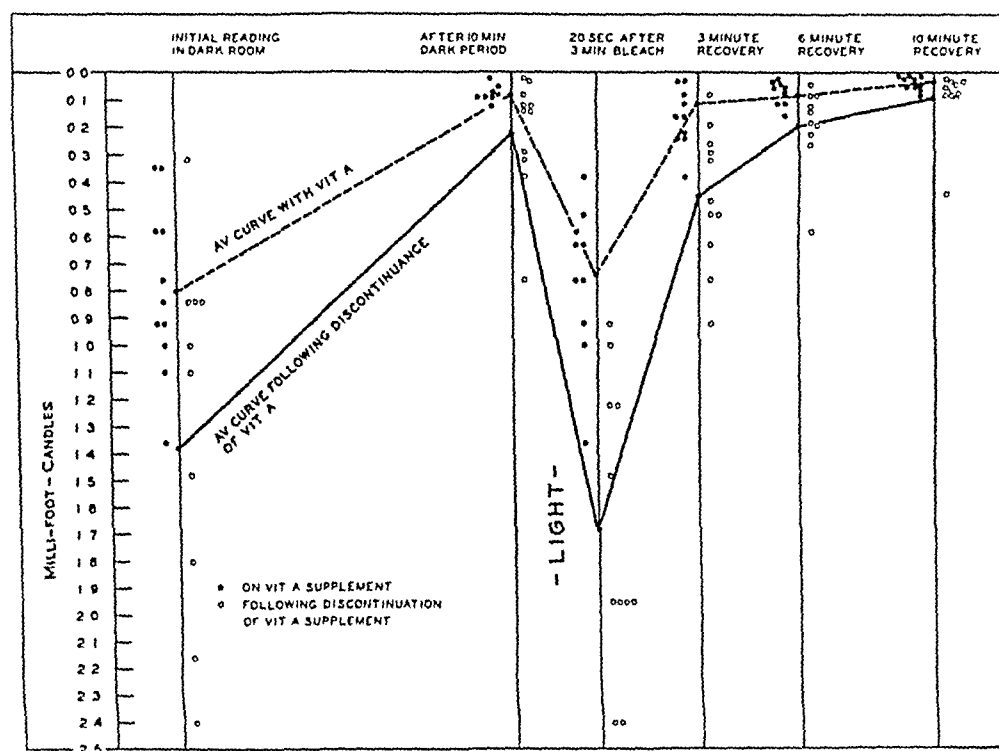


Fig. 6—The effect on biophotometer readings of removing vitamin A supplement from diabetic patients whose biophotometer readings had been maintained at normal or slightly subnormal levels by the supplement.

COMMENT

In connection with the previously mentioned observations the following work is of interest. Jegheis¹⁰ in 1937 placed normal subjects on diets containing 200 U S P units of vitamin A daily and in six days obtained lower biophotometer readings. After thirty-one days of the diet, improvement was noted twenty minutes after the patient was given an oral dose of 80,000 U S P units of vitamin A and the curves became normal after three days of feeding 100,000 units per day. Jegheis¹⁰ also reported that patients with diseased livers did not respond to carotene, but the administration of vitamin A resulted in

improved readings Wald, Jegheis and Arminio²⁵ in 1938, using the "adaptometer," noted that subjects deficient in vitamin A because of dietary restrictions responded to 100,000 U S P units of vitamin A by mouth in thirty minutes and to a similar amount of carotene in thirty-eight minutes. Smaller doses, of 17,000 U S P units of vitamin A and 20,000 units of carotene, gave similar results. It is of interest to note that patients treated in this way became hemeralopic two days after they discontinued taking the 100,000 unit doses of the supplement.

Although only 3 of our 20 patients studied were subjectively aware of night blindness, the biophotometer readings were all in a range compatible with some degree of night blindness.

SUMMARY

A control group of 20 subjects gave biophotometer readings comparable to the normal values obtained by other observers. Twenty patients with diabetes mellitus but with normal fundi who were tested in like manner by the same observer had biophotometer readings definitely suggestive of vitamin A deficiency in spite of blood carotene levels consistently above normal. Three of the group presented a history of night blindness, and 9 showed clinical evidence of mild vitamin A deficiency by cutaneous changes. Large doses of carotene for an adequate period failed to improve the biophotometer readings significantly in spite of increasing the already high blood carotene values. Comparable amounts of vitamin A given over similar periods produced significant improvement in the biophotometer readings. Removal of the vitamin A supplement from the diet of patients whose readings were held normal or nearly normal by the supplement resulted in immediate relapse to subnormal values. In this respect the patients reacted similarly to those studied by Wald, Jeghers and Arminio²⁵ then conditions relapsing promptly after the discontinuance of the large doses of vitamin A. The values for carotene in 90 per cent of the patients with diabetes mellitus studied were above normal. No definite correlation was noted between the blood cholesterol values and the changes induced during the course of the experiment.

CONCLUSIONS

A group of 20 patients with juvenile diabetes mellitus were studied, and all were found to have poor light adaptation by the Frober-Faybor biophotometer. Three of the group were subjectively aware of night blindness, and 9 showed cutaneous changes compatible with vitamin A deficiency.

²⁵ Wald, G. H., Jeghers, H., and Arminio, J. Experiment in Human Dietary Night Blindness, *Am J Physiol* **123** 732 (Sept.) 1938.

The daily administration of 60,000 U S P units of vitamin A, in the form of crystalline carotene dissolved in vegetable oil, for as long as fourteen days did not affect the light adaptation of the patients with diabetes mellitus

The daily administration of 60,000 U S P units of vitamin A to patients with diabetes mellitus, in the form of concentrated fish liver oils, caused their light adaptation to return to normal or nearly normal in periods ranging from three to twenty-one days

The cause of poor light adaptation in patients with juvenile diabetes mellitus appears to be an inability to convert carotene to vitamin A

SYNDROME OF PSEUDOBULBAR PALSY

AN ANATOMIC AND PHYSIOLOGIC ANALYSIS

ORTHELLO R. LANGWORTHY, M.D.

AND

FREDERICK H. HESSER, M.D.

BALTIMORE

Pseudobulbar palsy is a syndrome about which little is known in spite of the fact that it not uncommonly follows cerebral vascular accidents and other forms of neurologic disease. It is our purpose, therefore, to present an anatomic and physiologic analysis of this condition.

Magnus¹ first reported a case in which there were features characteristic of pseudobulbar palsy following multiple apoplectic attacks; he discussed the postmortem observations. Jolly² described a patient with multiple sclerosis and "progressive bulbar paralysis" whose bulbar nuclei were normal at autopsy; Barlow³ emphasized the relation of bilateral cortical lesions to the syndrome. Ross⁴ reviewed cases from an anatomic-functional point of view, and Oppenheim and Siemerling⁵ differentiated pseudobulbar from true bulbar palsy. Hunter and Robertson⁶ and Oettinger⁷ reported typical cases.

GENERAL CONSIDERATIONS

The designation "pseudobulbar palsy" is a misnomer. The term supranuclear bulbar paralysis would be more accurate. This term indicates the general position of the lesion and makes clear the distinction

From the subdepartment of Neurology, Johns Hopkins University, and the Medical Division of the Baltimore City Hospitals.

1 Magnus, A. Fall von Aufhebung des Willenseinflusses auf einige Hirnnerven, *Arch f Anat, Physiol u wissensch Med*, 1837, p. 258.

2 Jolly, F. Klinische Mittheilungen über einige in Folge des Feldzugs von 1870-1871 entstandene Psychosen, *Arch f Psychiat* **3** 442, 1872.

3 Barlow, T. On a Case of Double Hemiplegia, with Cerebral Symmetrical Lesions, *Brit M J* **2** 103, 1877.

4 Ross, J. Labio-Glosso-Pharyngeal Paralysis of Cerebral Origin, *Brain* **5** 145, 1882.

5 Oppenheim, H., and Siemerling, E. Die acute Bulbarparalyse und die Pseudobulbarparalyse, *Berl klin Wchnschr* **23** 791, 1886, abstracted, *Charite-Ann* **12** 331, 1887.

6 Hunter, W. K., and Robertson, M. E. A Case of Pseudobulbar Paralysis, *Rev Neurol & Psychiat* **10** 101, 1912.

7 Oettinger, B. A Case of Pseudobulbar Paralysis, Presenting Facial Spastic Movements Simulating Laughter, *M Rec* **84** 737, 1913.

between nuclear and central types of paralysis. However, the term pseudobulbar palsy is firmly entrenched in the literature.

Pseudobulbar palsy must be considered in relation to other causes of weakness of the bulbar muscles. These muscles may be paralyzed owing to disease involving the muscles themselves, their connections with the motor nuclei of the brain stem or their supranuclear control by the higher centers. Thus, myasthenia gravis appears to be primarily a disease of muscle. Progressive muscular atrophy and syphilitic basilar meningitis attack the lower motor neurons, causing secondary degeneration of the muscles and true bulbar palsy. Finally, bilateral injury of pathways from the cerebral motor cortex controlling the bulbar nuclei gives rise to the syndrome of pseudobulbar palsy.

It is evident that various factors may give rise to the lesions. Moreover, the corticobulbar fibers may be attacked at different points along their course. The anatomic changes, which must be bilateral, may occur in the cerebral motor cortices, the internal capsules, the cerebral peduncles or the pons.

The cardinal clinical features on which the diagnosis is based are grouped under difficulties of speech, difficulties of mastication and difficulties of deglutition, without signs of injury of the bulbar nuclei. Levy⁸ noticed that there is frequently intellectual enfeeblement. Loss of emotional control, manifested as forced laughing or crying, appears in typical cases, but the face in repose shows poverty of expression, sadness being the predominating note. Saliva may drip from the mouth, the jaw jerk is hyperactive. The patients eat slowly, owing to difficulties in mastication. The symptoms may come on suddenly or gradually, the rate of onset influences the clinical picture.

The corticospinal as well as the corticobulbar fibers are usually damaged, according to Tilney and Morrison,⁹ and quadriplegia results. Less often the extremities are affected unilaterally or in sequence. In certain cases the arms and legs are used fairly well, but even in such cases there are difficulties of coordination in the limbs and the patients walk with short steps.

UNILATERAL INJURY OF CORTICOBULBAR FIBERS

Unilateral interruption of the corticobulbar tract is usually associated with damage to the whole group of efferent fibers from the motor cortex. Loss of function in the bulbar muscles is slight and tends to be transient,

8 Levy, S. Les troubles de la parole au cours des états pseudobulbaires, *Rev. neurol.* 2: 289, 1930.

9 Tilney, F., and Morrison, J. F. Pseudobulbar Palsy Clinically and Pathologically Considered, with the Clinical Report of Five Cases, *J. Nerv. & Ment. Dis.* 39: 505, 1912.

since the nuclei of the cranial nerves are placed under the influence of both motor cortices by commissural neurons

Immediately after a cerebral vascular accident the eyes may be turned toward the sound side of the body so that it is impossible for the patient to look voluntarily toward the paralyzed side. However, if the gaze is fixed on an object and the head rotated passively, the eyes may be brought to the hemiplegic side. This deviation is demonstrable only for a few days, thereafter the eyes move well in all directions. For the same period the pupil is often larger on the paralyzed side.

Mastication is little impaired by unilateral injury of the corticobulbar fibers. On palpation of the contracting muscles a few days after the vascular accident some weakness may be noticed. When the patient opens the mouth widely there may be deviation of the jaw to the paralyzed side due to loss of strength in the pterygoid muscles on that side.

In hemiplegia the facial muscles show considerable paralysis. For the first few days after the onset these muscles often manifest a complete loss of tone and strength. It is impossible to close the eye tightly and no resistance is offered to passive raising of the upper lid. The cheek blows in and out with respiration. The facial folds are smoothed on the paralyzed side. Later there is considerable return of function particularly in the upper part of the face, as the muscles of this region appear to receive a greater degree of bilateral cortical innervation. Although tone is decreased in the facial muscles after the development of hemiplegia, it later returns and may be increased in the paretic muscles, so that the facial folds may be deeper than on the normal side.

The emotional responses of the facial muscles are integrated at a subcortical level, the exact centers and pathways are not yet known. Patients with loss of voluntary facial movement may respond to emotional stimuli on the paralyzed side even more markedly than on the normal.

The pharyngeal and laryngeal muscles show little loss of voluntary function in the presence of unilateral damage to the corticobulbar fibers. During the period of shock the voice may be weak and husky, later it is normal. The soft palate may move more strongly on the normal side, and as a result the uvula may be pulled to that side.

There is permanent weakness of the tongue in some hemiplegic patients. When this is present, the tongue deviates toward the paretic side.

BILATERAL INJURY OF THE CORTICOBULBAR FIBERS

As an example, one may consider a patient with cerebral vascular disease in whom hemiplegia developed first on one side and then on the other. He is examined after the period of shock has passed.

The pupils may or may not be equal in size, they are often small. Movements of the eyes are possible in all directions but are of limited range. There is difficulty in looking upward or in bringing the eyes far to the side. Usually accommodation is lost. The muscles of mastication contract weakly. The jaw jerk is hyperactive. The bilateral facial palsy is usually more marked in the lower portion, it is often possible to wrinkle the forehead slightly and to close the eyes.

Weakness of the pharynx and larynx gives rise to difficulties in swallowing and speaking. If the pseudobulbar palsy develops suddenly after a vascular occlusion, the difficulties of deglutition are particularly marked. In many instances the patient has to be tube fed for days. When the shock decreases, some power of deglutition returns. In case the pseudobulbar palsy develops gradually, the patient escapes complete loss of the power to swallow. Even so, he tends to choke easily. It is difficult to expel mucus from the pharynx, saliva tends to run from the corners of the mouth. Observation of the soft palate or the vocal cords reveals weakness of voluntary movement. Speech is often incomprehensible. The tongue can be protruded only a short distance.

BROADBENT'S HYPOTHESIS

Broadbent¹⁰ developed a hypothesis to explain the varying degree of paralysis of the muscles on the hemiplegic side. He noticed that all of the facial muscles show some degree of paralysis but that function is never entirely lost. There is slight paresis of the muscles of the forehead. For the first few days the orbicularis oculi muscle is obviously weak. The eye on the hemiplegic side cannot be closed independently, and voluntary contraction is less forceful on this side. In the perioral region the paralysis is most marked. The orbicularis oris muscle is less affected than are the straight muscles inserted in the lips and in the angles of the mouth. Perfect closure of the mouth is still possible.

Similarly, the masticatory, lingual and abdominal muscles show incomplete paralysis. The muscles with the mildest degree of weakness are those of the eye, neck, back and chest. The muscles with greatest loss of function are those the usual action of which is independent of the corresponding muscles on the opposite side of the body. The least parietic muscles are those which act only in unison with the contralateral group. In the case of symmetrically acting musculature it seems that the activating neurons have complete commissural connections whereby

10 Broadbent, W. H. An Attempt to Remove the Difficulties Attending the Application of Dr. Carpenter's Theory of the Function of the Sensori-Motor Ganglia to the Common Form of Hemiplegia, *Brit & For Med-Chir Rev* **37** 468 1866, A Lecture on the Theory of Construction of the Nervous System, *Brit M J* **1** 371 401 and 433 1876.

the coordination of bilateral muscular function is facilitated. This combination of neurons receives fibers from both motor cortices. It is usually activated by both cortices but is capable of excitation by either singly. Bilateral muscular response is more or less complete depending on whether the commissural connection is more or less perfect.

Observation of patients with almost complete destruction of both corticobulbar tracts shows that an astonishing amount of movement often is possible in the eyes, neck and trunk. This leads to consideration whether there is not a greater subcortical control of movement than is now suspected. The control of motor functions by the cerebral cortex becomes predominant only in the higher apes and in man. Other mammals show mild degrees of paralysis after removal of the motor cortices. Certainly essential activities, such as respiration, maintain efficient function without mediation of the higher centers.

EXPERIMENTAL PRODUCTION IN CATS OF A CONDITION RESEMBLING PSEUDOBULBAR PALSY

It is important to demonstrate that the difficulties of speech and swallowing, together with the loss of emotional control, result from bilateral damage to the corticobulbar tracts. This fact is not universally accepted. In cats a condition, which we consider similar to pseudobulbar palsy, has been produced by bilateral removal of the motor and premotor cerebral cortex (Langworthy and Kolb¹¹). It was found that electrical stimulation of the most lateral portion of the anterior cuneate gyrus gave rise to rhythmic chewing and lapping movements. When this area was removed on both sides, the cats showed abnormalities of feeding and emotional disturbances.

The animals at first made no effort to eat spontaneously. If a piece of meat was placed in the mouth and the jaw held closed, chewing movements began. The meat would eventually be swallowed if it was pushed far back in the pharynx. After three or four days the animals began to eat without assistance. They would snatch at food greedily until the whole mouth was filled and then swallow without chewing. Eating initiated emotional reactions manifested usually by loud purring but sometimes by growling.

The difficulties of drinking were more marked than those of eating and persisted for a longer time. On the first day after the operation it was customary to feed the cats from a spoon. Once the milk was introduced into the mouth, swallowing occurred. Lapping movements of the tongue often developed, these showed perseveration and usually continued when feeding was stopped. After two or three days the cats

11 Langworthy, O. R., and Kolb, L. C. The Experimental Production in the Cat of a Condition Simulating Pseudobulbar Palsy, *Am. J. Physiol.* **111** 57, 1935.

would make unsuccessful attempts to drink from a dish. They insisted on putting their paws into the fluid. Some opened and closed the mouth and attempted to drink without using the tongue. Lapping became reestablished only after ten days to two weeks, and even then coordination of lapping, swallowing and breathing was abnormal. Often the cats would bite on the glass rim or continue the lapping movements away from the milk or outside the dish. At times they would stand rigid in one position and stare fixedly into space for considerable periods. This appeared to be a cataleptic phenomenon.

PHYSIOLOGIC ANALYSIS OF THE SYMPTOMS OF PSEUDOBULBAR PALSY

The abnormalities associated with pseudobulbar palsy may be classified under the headings of shock, loss of function and release of function. The difficulties in swallowing are certainly more marked immediately after the apoplectic onset of the syndrome, persist for the first few days and then slowly ameliorate; this is a manifestation of shock. There are always some difficulty of deglutition and poor coordination of swallowing with breathing. This signifies a loss of function. The abnormal emotional responses may be taken as an example of release of function.

1 *Swallowing*—Swallowing is coordinated largely at a reflex level in cases of pseudobulbar palsy. Beever¹² described the case of a man who was unable to open his mouth voluntarily to admit food. A physician sat at the foot of the bed and went through the motions of yawning, initiating a reflex of similar activity in the patient. When the latter's mouth was open, the nurse inserted food.

Because of the weakness of the pharyngeal muscles, the patients have difficulty in expelling the mucus which tends to collect in the throat. The coordination between breathing and swallowing is poor, so that food may enter the bronchi and cause bronchopneumonia. Since the patients do not swallow readily, saliva accumulates and drips from the mouth.

2 *Speech*—During the period of shock speaking is impossible. Later the speech disturbances are of many types. Phonation is always poor because of weakness of the articulating muscles due to loss of function. The mechanism of release may sometimes be observed as increased tone in the laryngeal muscles and may manifest itself as a lack of flexibility in sound production. With a slow onset of pseudobulbar palsy, such as is seen in multiple sclerosis, speech is more severely affected than is swallowing. Secondary involvement of other pathways in the nervous system tends to modify the speech disturbances. If the syndrome is produced by pontile lesions, the cerebellar pathways as well as the corticobulbar tracts are injured, and a cerebellar type of dysarthria results.

12 Beever, C. E. A Case of Pseudobulbar Paralysis with Complete Loss of Voluntary Respiration, *Archiv f. d. neurol. Inst. u. d. Wien Univ.* 15: 537, 1907.

Levy⁸ pointed out that there is abnormality both in the rhythm and in the timbre of speech. Dissociation between voluntary and automatic speech is manifested as a type of repetition termed palilalia. Loss of the normal chant or melody of language makes the patients speak in short interjections which are more or less indistinct, monotonous and explosive. Speech is pitched in an unusual and difficult register, the patients use short words and speak with abnormal rapidity. There is a tendency to precede any initial vowel with an aspirate. Difficulty is found in pronouncing labial and labiodental sounds. The voice frequently has a nasal quality. When these troubles reach their maximum anarthria occurs.

Patients with pseudobulbar palsy sometimes show a loss of tone in the palate and absence of the palatal reflexes. Often one or both vocal cords are fixed in partial adduction. The movements of the diaphragm are irregular, jerky contractions being superimposed on the normal rhythm. There is a tendency toward equality of the inspiratory and the expiratory phase. The disturbances in phonation are to be explained in part on the basis of these respiratory factors. In summary, it may be said that patients show varying abnormalities in speech, depending on the amount of strength of voluntary control lost and the condition of increased or decreased tone present in the muscles of speech. After the period of shock has ended, increased tone may appear in the laryngeal and thoracic musculature and may influence articulation even further.

3 *Respiration*—Jackson¹³ in 1895 observed that Cheyne-Stokes respiration is observed frequently in patients with bilateral injury of the corticobulbar tracts. He stated the belief that the respiratory center in the medulla is released from cortical control and overacts to normal blood-borne chemical stimuli in a rhythmic manner. Other observers (Bucy and Case¹⁴) demonstrated the cortical control of respiratory activity in the dog and in man by delimiting cortical areas where stimulation caused marked deceleration or arrest of respiration.

We have studied and recorded rhythmicity of respiratory excursions in pseudobulbar palsy (Grimmer, Hesser and Langworthy¹⁵). A typical record is shown in figure 1. Simultaneous pneumograph tracings were taken from each side of the chest, time is recorded in five second intervals. The upstroke indicates inspiration. Drugs, such as coramine

13 Jackson, J. H. Superior and Subordinate Centers of the Lowest Level, *Lancet* **1** 476, 1895.

14 Bucy, P. C., and Case, T. J. Cortical Innervation of Respiratory Movements, *J. Nerv. & Ment. Dis.* **84** 156, 1936.

15 Grimmer, R. V., Hesser, F. H., and Langworthy, O. R. Rhythmic Variation of Respiratory Excursion with Bilateral Injury of Cortical Efferent Fibers *Arch. Neurol. & Psychiat.* **42** 862 (Nov.) 1939.

(a 25 per cent solution of pyridine betacarboxic acid diethylamide) or aminophylline (theophylline with ethylene diamine U S P), as well as the administration of oxygen or carbon dioxide, tended to abolish the periodicity in these cases

4 *Emotional Release*—The explanations for emotional release giving rise to forced laughing and crying have never been satisfactory, the most logical discussion has been presented by Wilson¹⁶ Pathologic laughing and crying refer to the manifestation of involuntary and irresistible emotional outbursts as a consequence of cerebral lesions

The stimuli which arouse the exaggerated, forced, involuntary and uncontrollable laughing or weeping are often inadequate as well as

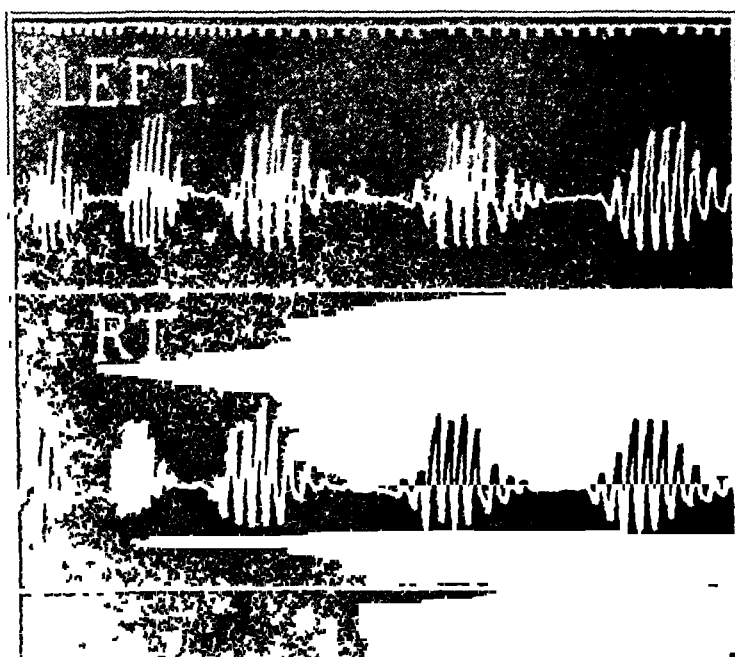


Fig 1—Bilateral pneumographic tracings of periodic breathing in a case of pseudobulbar palsy (Dr R V Grimmer provided these tracings and those in figure 3)

inappropriate In not a few cases the emotional exhibition, though elicited by trifling but appropriate impulses, is excessive and out of proportion to the impressions originating it In others, a stimulus of a particular quality is followed by an emotional outburst of a contradictory sort The visible emotion need not correspond to the patient's real feelings at the time

In some instances the emotional response is invariable, whatever the stimulus Some of the sufferers do nothing but laugh, others can

¹⁶ Wilson, S A K Pathological Laughing and Crying, J Neurol & Psychopath 4 299, 1924, Modern Problems in Neurology, New York William Wood & Company, 1929, chap 12

only weep. A generalization suggests that patients having multiple sclerosis with pseudobulbar palsy manifest cheerfulness, whereas in arteriosclerotic patients sadness seems to predominate.

At the same time, the emotional display is a genuine show of feeling which no one can doubt. It differs from normal emotional reactions in its inevitability, frequency and uncontrollable character, in the occasionally contradictory relation of cause and effect and in the extreme facility with which it is induced, in expression and accompaniments it is identical. Photographs of 3 patients laughing and crying are presented (fig. 2). The first patient (figs. 2 *A* and 2 *B*) had periods of laughing and crying, the second (figs. 2 *C* and 2 *D*) only laughed. The third patient (figs. 2 *E* and 2 *F*) cried spontaneously or at the slightest verbal stimulus.

In laughter there is participation of the facial and respiratory musculatures as well as of other bodily mechanisms. The automatic rhythm of respiration is interrupted by prolonged inspirations followed by short and broken expirations. Coupled with these respiratory movements are laughter sounds of laryngeal origin and of varying character and pitch. If laughter is overwhelming, other muscles besides those of the face and respiratory apparatus are implicated, in fact, there may be much concomitant movement of the trunk and extremities.

Crying may utilize either the inspiratory or the expiratory phase of the cycle. There is a marked vasoconstrictor effect which explains the pallor, sunken features and sensations of cold and lassitude. Study of facial and respiratory movements is the basis for an analysis of the mechanism of response. However, some of the patients change rapidly from laughing to crying, and it is somewhat difficult on observation to be sure what emotion they are expressing. In figure 3 simultaneous spirographic and pneumographic tracings taken during one outburst of forced crying are presented. Inspiration is recorded as a downstroke in the spiograph which oscillates with movements of the air column. At the same time an upstroke occurs in the pneumograph, representing epigastric movement. Time is recorded in seconds. It will be noticed that crying began a little before the point *A*, halfway through a quiet expiration. Rapid, spasmodic, rhythmic but irregular contractions of the expiratory musculature followed for seventeen seconds. According to the spiograph, a few of the early contractions forced air past the closing glottis and caused audible sobbing to the point *A*, thereafter the glottis closed and weeping was silent. An apparent inherent tremulousness is present in the pneumograph tracing during quiet breathing and may represent persistent "undercurrent" sobbing respiration. These movements are too rapid to be transmitted aortic impulses.

The facial muscles have three distinct types of action—reflex (as respiratory muscles), emotional (as muscles of expression) and voluntary (as muscles subject to cerebral control). The ease with which the reflex and emotional control over the facial musculature creeps through or escapes from voluntary repression is frequently conspicuous in normal persons. The point at which this occurs retains a threshold value for

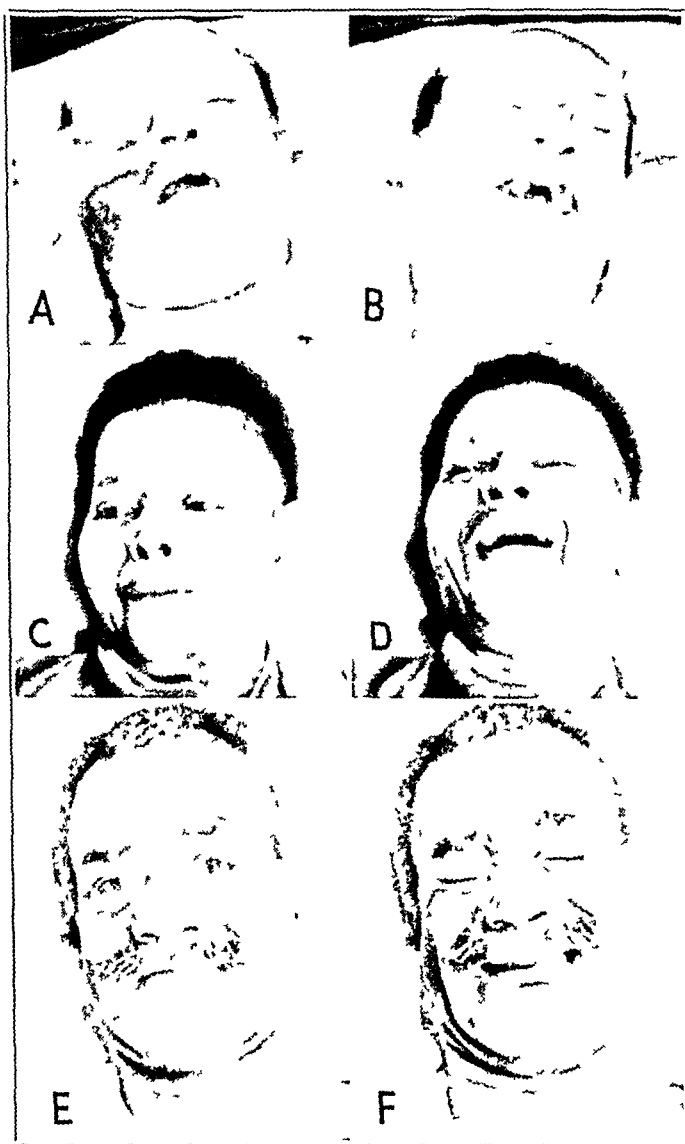


Fig 2—*A*, patient with hypertensive and syphilitic vascular disease, bilateral cerebral thromboses, double hemiparesis and pseudobulbar palsy. Note the atonic face, with predominant sadness. *B*, same patient, exhibiting pathologic laughing. *C*, another patient with hypertensive and syphilitic vascular disease, bilateral cerebral thromboses, double hemiparesis and pseudobulbar palsy, showing the tendency to a spastic facies with deepened nasolabial furrows and predominant cheerfulness. *D*, same patient, exhibiting forced laughing. *E*, patient with hypertensive vascular disease, multiple cerebral thromboses, double hemiparesis and pseudobulbar palsy, also manifesting a spastic facies but showing predominant sadness. *F*, same patient, showing forced crying.

each patient, balancing the strength and type of the underlying emotional or reflex stimulus against a labile volitional force that is subject to fluctuations of attention as well as to various physiologic and anatomic changes

Nothnagel¹⁷ postulated the existence of an emotional reflex pathway distinct from the corticobulbar fibers. He stated the opinion that the optic thalamus forms the origin of the efferent tract. No anatomic evidence for this theory has been found.

Brissaud¹⁸ assumed that the integrity of the thalamus is essential for the appearance of spasmodic laughing and crying. He stated the belief that thalamic activity is ordinarily held in check by a fronto-thalamic tract running in the anterior limb of the internal capsule.

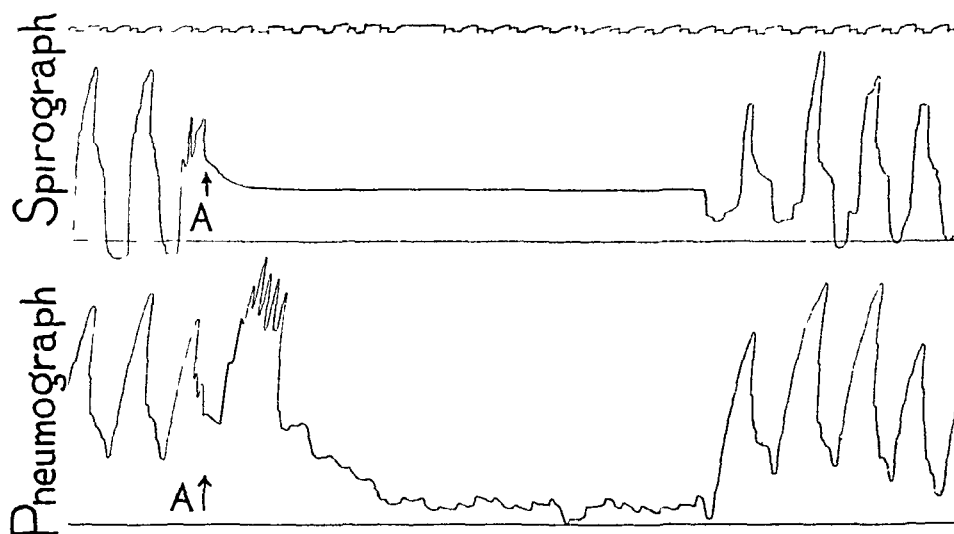


Fig. 3—Simultaneous spirographic and pneumographic tracings made during one outburst of forced crying.

Wilson,¹⁶ in 1929, based his theory of mimetic overreaction on the participation of both the facial and the respiratory mechanism. Bell¹⁹ called the seventh nerve "the facial nerve of respiration," and paralysis of the lower part of the face was described by him as "paralysis of the respiratory functions of the facial." One may speak, therefore, of the faciorespiratory mechanism. The automatic activity of this mechanism is set aside voluntarily when one deliberately holds the breath or takes deep breaths and more or less voluntarily when one pants, coughs,

17 Nothnagel, H. *Topische Diagnostik der Gehirnkrankheiten*, Berlin, A. Hirschwald, 1879.

18 Brissaud, E. *Leçons sur les maladies nerveuses*, edited by H. Meige, Paris, G. Masson, 1895.

19 Bell, C. *The Nervous System of the Human Body*, ed. 3, London, H. Renshaw, 1844.

yawns or sighs. Its activity is set aside involuntarily when one is convulsed with laughter or gives way to crying. One obtains, therefore, a glimpse of a triple control over faciorespiratory movements.

The paths of voluntary impulses to facial and respiratory muscles are undoubtedly the corticobulbar and corticospinal tracts. In particular, the fibers from the operculum and the lower end of the precentral gyrus running in the genu of the internal capsule, convey the impulses to the bulbar nuclei. Lloyd's case, to be described later, bears out this concept. Injury of the corticobulbar fibers impairs volitional control over the muscles concerned in emotion, with the result that the involuntary action of the same muscles tends to be overactive. The more severe the volitional faciorespiratory paralysis, the more exaggerated is the loss of emotional control. Emotional activity is often distinctly increased on the paretic side in patients with hemiplegia.

There is little evidence for the exact localization of the faciorespiratory involuntary control. Brown²⁰ found a small area in the mesencephalon of the chimpanzee, between the internal border of the red nucleus and the midline, which on stimulation gave responses similar to laughing. Likewise, the experimental work of Bard²¹ on sham rage in cats, as well as that of Lilienthal and Otenasek²² on polypnea in decorticate animals, demonstrates the release of diencephalic mechanisms controlling the emotional and reflex responses of the faciorespiratory muscles.

5 *Jaw Jerk*—An unusually active jaw jerk is an important sign of bilateral injury to the corticobulbar fibers. This reflex, like all other deep reflexes, becomes exaggerated when released from cerebral control.

6 *Allied Phenomena*—Mental deterioration of varying degrees and types is frequently seen, especially in old arteriosclerotic persons with progressive diffuse cortical softening. Certain patients have cataleptic periods, during which they remain perfectly quiet with the eyes fixed. The sucking reflex is often demonstrable. Other patients may exhibit tonic perseveration, forced grasping and groping, recently shown to depend primarily on lesions of the premotor cortex. Figure 4 shows a patient with pseudobulbar palsy in whom forced grasping as well as the sucking reflex was demonstrable. Some patients have an unusually large appetite and eat ravenously.

20 Brown, T. G. Note on the Physiology of the Basal Ganglia and Mid-Brain of the Anthropoid Ape, Especially in Reference to the Act of Laughter, *J. Physiol.* **49** 195, 1915.

21 Bard, P. On Emotional Expression After Decortication with Some Remarks on Certain Theoretical Views, *Physiol. Rev.* **41** 309, 1934.

22 Lilienthal, J. D., and Otenasek, F. J. Decorticate Polyneic Panting in the Cat, *Bull. Johns Hopkins Hosp.* **61** 101, 1937.

VARIATIONS IN THE SYNDROME AS RELATED TO THE
LOCATION OF THE CEREBRAL INJURY

The three chief symptoms of the syndrome, difficulties of speech, difficulties of swallowing and emotional instability, may be developed in varying degrees in individual patients and at different stages of the



Fig 4—*A*, patient with multiple cerebral thromboses, right hemiplegia, left hemiparesis and pseudobulbar palsy, demonstrating forced grasping *B* and *C*, same patient, showing the sucking reflex

disease. Other associated abnormalities are dependent on injury of other pathways in the brain. These modify the primary abnormalities and often serve to localize more accurately the disease process.

Symmetric areas of softening of the motor cortex in the lower portion of the prefrontal area and the operculum destroy the cerebral control

of the bulbar muscles. This type of lesion may result from embolism or thrombus formation. In cases of cortical softening the corticobulbar fibers may be damaged selectively, leaving the corticospinal pathway practically or wholly uninjured.

Alajouanine and Thurel²³ described the clinical picture of pseudobulbar palsy produced by bilateral lesions of the cerebral motor cortex. The paralysis is limited to the masticatory muscles and those of the face, larynx, pharynx and tongue, there are weakness and restriction of ocular movements. Involvement of the extremities is slight and transient. Atonia is usually present, which explains why laughing and crying lack their usual spasmodic character.

The lesions responsible for pseudobulbar palsy occur perhaps most frequently in the internal capsules. A case reported by Lloyd²⁴ was unique in that there were bilateral vascular lesions confined to the genu of each internal capsule and adjacent lenticular nucleus creating typical pseudobulbar palsy without manifest involvement of the corticospinal tracts. Often there are diffuse small areas of encephalomalacia dependent on arteriosclerosis. These softenings are found also in the basal ganglions and may give rise at the same time to the parkinsonian syndrome. Thus diffuse rigidity may form a background for the pseudobulbar palsy. The face may show the immobility associated with the parkinsonian syndrome as well as the characteristic features of pseudobulbar palsy. It must be realized, of course, that parkinsonian rigidity in itself gives rise to difficulties of speaking and swallowing. The tremor may be evident in speech.

Pontile lesions may be responsible for the syndrome. Injury of cerebellar pathways as well as of the corticobulbar tracts may be found. The incoordination of speech and breathing is suggestive of that associated with isolated damage to the cerebellum.

The sharp differentiation of these various secondary manifestations from the primary symptoms of pseudobulbar palsy is seldom made. We maintain that the characteristic findings of difficulty in speech and swallowing combined with emotional instability are always dependent on bilateral injury of the corticobulbar fibers.

DISEASE PROCESSES WHICH OFTEN PRODUCE THE SYNDROME OF PSEUDOBULBAR PALSY

In the majority of cases pseudobulbar palsy results from cerebral vascular lesions. Arteriosclerosis or syphilitic vascular disease with thrombotic softenings may be demonstrated in the brain in many cases.

23 Alajouanine, T, and Thurel, R. La diplegie faciale cerebrale, forme corticale de la paralysie pseudobulbaire, *Rev. neurol.* 2: 441, 1933.

24 Lloyd, I. H. Pseudobulbar Palsy, *Internat. Clin.* 4: 210, 1908.

Thrombosis of the median group of fine pontile and vertebral arteries tends to produce the syndrome. In certain cases of cerebral vascular disease, especially the more acutely developing conditions, the typical features of pseudobulbar palsy may be strongly marked for a time and may then regress. There is a small group of cases in which the syndrome is caused by tumors or by infectious processes.

Patients with multiple sclerosis may have pseudobulbar palsy, particularly in the later stages of the disease, more often only a portion of the syndrome is present. Emotional instability is extremely common. Disturbances of speech and sometimes difficulties in swallowing occur. Bilateral involvement of the corticoefficient fibers is most commonly due to plaques in the pons, so that difficulties of speech and swallowing in these cases may be modified by the incoordination commonly associated with injury of the cerebellum.

Certain familial diseases may produce the syndrome of pseudobulbar palsy. In Friedreich's ataxia there is involvement of the corticobulbar and corticospinal tracts. Forced laughing and crying are strongly developed. Signs of cerebellar disease are combined with the syndrome. Syringobulbia may produce damage to the brain stem and give rise to emotional instability and to difficulties in speaking and swallowing.

True bulbar and pseudobulbar palsy occur together in amyotrophic lateral sclerosis. In this disease there is degeneration of the lower motor neurons in the nuclei of the cranial nerves and anterior columns of the spinal cord as well as degeneration of the Betz cells. In certain cases the lower motor neurons degenerate first and more severely, in others the corticobulbar and corticospinal pathways bear the brunt of the damage. In the latter instances typical symptoms of pseudobulbar palsy are observed. Often, with the whole syndrome present it is possible also to demonstrate fibrillations and atrophy in the facial and masticatory muscles and in the tongue.

DIFFERENTIAL DIAGNOSIS

Conditions in which weakness of the muscles or damage to the lower motor neurons of the cranial nerves occur alone must be differentiated from pseudobulbar palsy. In such conditions emotional instability is absent but there may be profound difficulties in speech and deglutition. This is true of myasthenia gravis, progressive muscular atrophy or any condition involving the medullary motor components. Pseudobulbar palsy is differentiated by its frequent association with hemiplegia or quadriplegia, the absence of wasting, fibrillation or reaction of degeneration in the muscles supplied by the cranial motor nuclei, retention and frequent exaggeration of the jaw jerk and the characteristic phenomena of emotional release. The syndrome may occur with true bulbar palsy

in which case interpretation is more difficult. Likewise, a condition of pseudobulbar palsy may be obscured by the shock immediately following a cerebral vascular accident or by increased intracranial pressure. In a recent paper, Karnosh and Connor²⁵ stated significantly: "Pathologic grimacing is a transitory phenomenon, frequently dependent on the locale of the lesion and clearing as the hemiplegia improves. It may therefore escape detection and, in many cases of central nervous system syphilis, be regarded as a manifestation of the emotional derangement of dementia paralytica."

25 Karnosh, L. J., and Connor, W. H. Syphilitic Pseudobulbar Palsy with Compulsive Weeping, *Am J Syph, Gonorr & Ven Dis* **20** 115, 1936.

PURPURA HAEMORRHAGICA DUE TO INGESTION OF SEDORMID (ALLYLISOPROPYL- ACETYLCARBAMIDE)

EXPERIMENTAL OBSERVATIONS AND REPORT OF A CASE

ERNEST H FALCONER, M D

AND

IRWIN C SCHUMACHER, M D

SAN FRANCISCO

In 1933, Dennig¹ reported 3 cases of purpura haemorrhagica due to oral administration of iodifix, a preparation containing iodine. One of the patients, a woman aged 64, after recovery from iodine purpura had two distinct relapses, each following the use of 1 tablet of sedormid (allylisopropylacetylcarbamide), a drug that she had not used previously. From 1933 to October 1938 reports of instances of purpura haemorrhagica following the use of sedormid² appeared in rapidly increasing

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From the Department of Medicine, University of California Medical School

1 Dennig, H. Thrombopenische Purpura nach Jodeinnahme, *Munchen med Wchnschr* **80** 562 (April 14) 1933

2 (a) Loewy, F. E. Thrombopenic Haemorrhagic Purpura Due to Idiosyncrasy Towards the Hypnotic Sedormid. Allergotoxic Effect, *Lancet* **1** 845 (April 21) 1934. (b) Graubner, W., cited by Hadorn^{2d}. (c) Stern, R. Psychose bei Purpura cerebri infolge Sedormidüberempfindlichkeit, *Wien klin Wchnschr* **49** 1288 (Oct 16) 1936. (d) Falta, W. Fall von Sedormidpurpura, *ibid* **49** 798 (July 19) 1936. (e) König, F., in discussion on Falta^{2d}. (f) Decastello, A., in discussion on Falta^{2d}. (g) Glasz, E., in discussion on Falta^{2d}. (h) Pollacsek, K. F., in discussion on Falta^{2d}. (i) Hadorn, W. Purpura thrombopenica durch Sedormid, *Schweiz med Wchnschr* **17** 1273 (Dec 12) 1936. (j) Vogl, A. Thrombopenische Purpura nach Sedormidgebrauch, *Wien klin Wchnschr* **48** 908 (Jul 5) 1935. (k) von Lauda, E., in discussion on Vogl, A. Die Pathogenese der akuten thrombopenischen Purpura, *Wien med Wchnschr* **86** 1118 (Oct 3) 1936. (l) Boas, E. P., and Erf, L. A. Thrombocytopenic Purpura Following Medication with Sedormid (Ureide Preparation) and with Phenobarbital, *New York State J Med* **36** 491 (April 1) 1936. (m) Peck, S. M., Rosenthal, N., and Erf, L. A. Value of Prognostic Venom Reaction in Thrombocytopenic Purpura, *J A M A* **106** 1783 (May 23) 1936. (n) Mettier, S. R., and Stone, R. S. Effect of Roentgen Ray Irradiation on Platelet Production in Patients with Essential Thrombocytopenic Purpura Haemorrhagica, *Am J M Sc* **191** 794 (June) 1936. (o) van Andel, P., and Groen, J. Thrombopenic Purpura (Werlhof's Disease) After Use of Sedormid, *Nederl tijdschr v geneesk* **81**

numbers, as evidenced by our having found, in the literature covering this period of approximately five years, reports of 41 cases. Including our reported case, the total number of cases at the time of writing (November 1938) is 42. We have prepared a table (table 1) setting forth the names of the authors and their reports of cases during the period mentioned. Pertinent data in connection with these published cases have been tabulated for comparison and study. Some of the details we are interested in are lacking, but we believe all of the 41 cases are well authenticated instances of thrombopenic purpura due to ingestion of sedormid.

The table shows 24 women and 12 men, as indicated by the reports in which the sex was stated. Of the women, 20 were over 35 years of age, 14 were over 48, and in 2 instances the age was not stated. Of the men, 1 was 32, 2 were 43, and the remaining 9 were over 50. In 4 cases neither sex nor age was stated. The cases indicate an increased susceptibility to the purpuric manifestations of sedormid among the older age groups in both sexes. In the instances in which platelet counts were made at the time of the purpuric manifestations, the number per cubic millimeter was usually below 80,000. There were 2 exceptions to this. In case 31 (reported by Hoffman, Kahn and Fitzgibbon^{2r}) the platelet count was 152,000 on the second day after taking $\frac{1}{2}$ tablet of sedormid. However, the attack was reproduced by the ingestion of 1 sedormid tablet, and the number of platelets recorded the morning following the taking of the sedormid was 59,000 per cubic millimeter. In case 38 (reported by Hill^{2v}) the platelet count was 180,000 on the day following ingestion of the last sedormid tablet. As indicated in table 1, the white cell count during the attack varied from 4,900 to 5,600 per cubic millimeter in 5 cases and from 6,800 to 10,400 in 7 cases and was 20,000 in 1 case. The hemoglobin determinations and the red blood cell counts are not recorded in table 1, since no information is available concerning the presence of anemia prior to the attack. There are too few observa-

3348 (Jul 10) 1937 (p) Kramer, P. H. Purpura Hemorrhagica After Use of Sedormid *ibid* **81** 3345 (Jul 10) 1937 (q) Lieberherr, W. Zur Kenntnis der Purpura thrombocytopenica beim Gebrauch von Sedormid, *Med. Klin.* **33** 475 (April 2) 1937 (r) Hoffman, A. M., Kahn, I., and Fitzgibbon, J. P. Thrombocytopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), *I. A. M. A.* **110** 725 (March 5) 1938 (s) Moody, A. M. Thrombocytopenic Purpura Following Use of Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), *ibid* **110** 726 (March 5) 1938 (t) Torrens, J. Purpura Following Sedormid, *Lancet* **1** 749 (March 26) 1938 (u) Joekes, T. Purpura Haemorrhagica (Werlhof's) After Taking Sedormid *ibid* **2** 305 (Aug 6) 1938 (v) Hill, D. B. Thrombopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), *I. A. M. A.* **111** 1459 (Oct 15) 1938 (w) Naegeli, O. Differentialdiagnose in der inneren Medizin ed 2, Leipzig, Georg Thieme, 1936 cited by Joekes^{2u} Denning¹

tions recorded on the marrow of the sternum to permit any conclusions. Recovery is apparently rapid as soon as the drug is discontinued. In the majority of the cases from three to eight or ten days has seen complete clearing of the purpura, with cessation of bleeding. Treatment, including such measures as roentgen therapy, administration of vitamin C, blood transfusion, giving of calcium or intramuscular administration of liver extract, apparently has not shortened the interval of recovery. The amount of sedormid necessary to cause sensitization varies greatly. After sensitization the amount of the drug necessary to reproduce the purpuric and hemorrhagic phenomena is small, usually 1 or 2 tablets.

REPORT OF CASE

History—M. G., a white woman aged 26, single, was admitted to the University of California Hospital on June 19, 1937, complaining of small dark spots and larger "black and blue" areas, scattered on and beneath the skin of her entire body. Her symptoms began about May 29 (three weeks before admission to the hospital), at which time she noted small reddish spots, "like grains of red pepper," scattered over her lower extremities. Successive crops of spots of this type appeared until all the skin of the body was involved. In addition, large "black and blue" areas, a few 6 or 8 cm. in diameter, appeared over the lower part of the abdomen and the lower extremities. A few of these ecchymotic areas were very tender on pressure. At the time of entry there was slight bleeding from the gums. The last four menstrual periods had occurred one week earlier than usual and the flow had been more profuse.

She had had an operation at the age of 19 for removal of the appendix and for suspension of the uterus. At the age of 15 she began to suffer from hay fever, which recurred every spring when she was in the San Joaquin Valley and San Francisco Bay area. She began having bronchial asthma at the age of 22. For the first two years it was experienced only in the spring and accompanied the hay fever. During the past year, however, it was present more or less continuously, having failed to clear up at the end of the hay fever period of spring. The asthmatic attacks were especially troublesome at night, when the wheezing and coughing were severe. Skin tests at the age of 15 showed positive reactions to pollen, but no pollen hyposensitization was ever attempted. In addition to the hay fever, bronchial asthma and purpura, the only allergic history obtainable was that of the invariable production of an asthmatic attack by the drinking of beer. In the patient's opinion, her daily diet has been somewhat restricted. It has included orange or tomato juice, graham crackers, coffee, soups, canned beans, milk, sandwiches, salads, vegetables, meats and desserts. For the past year the only medication aside from sedormid had been pills of ferrous carbonate U. S. P. The history of sedormid medication went back to a period about six months before admission, when the patient began to take 1 to 2 or 3 tablets a week for sleep, depending on the frequency and severity of her asthmatic attacks. During her midterm college examinations (April 1937) she took about 4 tablets in one week. At this time she noted a slight scattering of petechiae during her menses. Two months later, she again took 4 or 5 tablets during one week (May 21 to 29), after which the attack occurred for which she was admitted to the hospital. However, she continued to take 1 tablet nightly up to the day of admission.

In the hospital she was given a high vitamin, unrestricted diet, 0.6 Gm of reduced iron four times daily and 4 Gm of calcium gluconate three times a day. During the first five days in the hospital the patient was given 0.05 Gm of amytal each night. During the first nine days in the hospital she received 0.025 Gm of ephedrine sulfate for eleven doses and two injections of a 1:1,000 dilution of epinephrine, 0.5 and 0.25 cc, respectively.

Dermal and intradermal tests showed many positive reactions to spring, summer and fall pollens. No positive reactions were obtained to house dust, animal danders, miscellaneous inhalants, eggs, milk, the common cereals, meats, vegetables or fruits.

Physical Examination—Petechiae were found scattered over the trunk and extremities. A small hematoma was observed beneath the right lower eyelid, and large ecchymotic areas were present over both arms and the region of the iliac crests. On both thighs were large ecchymotic areas from 8 to 10 cm in diameter, and over the lower extremities similar areas from 6 to 8 cm in diameter (fig 1). Some areas over the lower extremities were very tender on moderate pressure.

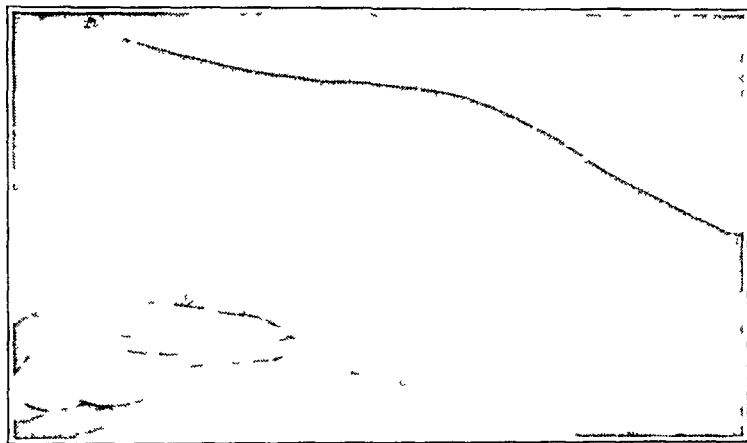


Fig 1—Ecchymoses on the left thigh and lower part of the abdomen

The blood pressure was 110 systolic and 65 diastolic. The heart was not enlarged, and there were no murmurs. Neither spleen nor liver was felt. An examination of the pelvis revealed nothing abnormal. The lungs were normal.

Laboratory Data—On June 21 the ascorbic acid content of the plasma was 0.78 mg per hundred cubic centimeters. The results of Dalldorf capillary fragility tests on the upper part of the left arm showed showers of petechiae with —20 cm pressure, 30 to 40 petechiae, with —15 cm pressure and 6 to 8 petechiae with —10 cm pressure.

The Kolmer modification of the Wassermann and Kahn tests of the blood gave negative reactions. On June 20 the urine showed no red blood cells. On June 24 the stool gave a negative reaction to the test for occult blood. On June 20 the blood clotting time (Lee and White) was three and one-half minutes, with a bleeding time (Duke) of six minutes. The platelet count on June 23 was 130,000 per cubic millimeter.

Experimental Procedures—On June 26 0.5 Gm of sedormid was dissolved in 5 cc of distilled water. A piece of blotting paper saturated with this solution was placed on the skin with adhesive tape. After forty-two hours no reaction of any kind had taken place locally. During this period there was no significant alteration

TABLE 1—Cases of Purpura Haemorrhagica Due to Sedormid in the Literature from 1933 to 1938

Author	Case	Sex	Age	No of Platelets A Height of Attack B After Recovery		Effects on Blood Cells Other Than Platelets	Previous Allergy or Purpura	Approximate Time for Recovery	Treatment	Amount of Sedormid Taken Before Purpura Appeared	Attacks Reproduced Experimentally or Accidentally
Dennig ¹ (1933)	1	M	64	A 48,000, 12/14/33 R 15,000, 12/15/33 R 50,000, 12/23/33			Sensitive to iodine			Two relapses each time after use of 1 tablet	Yes
Loewy ^{2a} (1934)	2	M	61	A 22,000, 10/ 5/31 R 360,000, 10/16/31		A White cells 9,600, anemia, myelo- cytes present R 9,600	Irritable colon, pruritus	6 days	Transfusion	1-2 tablets frequently over period of 3 years	Yes
	3	F	60	A 28,000 R Normal		A White cells 6,800, eosinophils 9 4%, slight anemia, neutropenia	Nervous indiges- tion	7 days	None	1 2 tablets per night for 5 6 weeks	No
	4	F	51	A 36,000, 2 days after drug				No further spots after stopping drug	Transfusion	½ 1 tablet repeatedly for 1 year	No
Graubner ^{2b} (1934)	5	M	59	Platelets dimin- ished						3 tablets daily for 8 months	Yes
Stern ^{2c} (1936)	6	M	63				None mentioned	8-10 days	None	1931 several tablets, no symptoms, 1934 1 tablet, purpura, June 1935 2 tablets, chills, fever, purpura, psychosis	No
Talta ^{2d} (1936)	7	F	57	A 20,400, 4/25/36 R 417,500, 5/ 4/36		White cells 5,400	None mentioned	Immediately after cessa- tion of drug	None	2½ tablets daily for sev- eral weeks without symp- toms, stopped drug for 2 weeks, on taking it again had attack purpura haemorrhagica	Yes
König ^{2e} (1936)	8	F	68				Intestinal hem- orrhage		None		No
Decastello ^{2f} (1936)	9	M	55	A 27,000, 3/28/36 R 125,000, 4/ 3/36					Ascorbic acid (cancan)	21 tablets in 14 days	No
Glasz ^{2g} (1936)	10	M	68	Purpura occurred on initial use of drug						1 tablet	No
Pollacsek ^{2h} (1936)	11	F	Young girl	No platelet count made				Severe attack with rapid recovery	None	Unknown number of tab- lets, with suicidal intent	No

								8 9 days	None	1 2 tablets per week for 11 weeks	
Hadorn ²¹ (1936)	12	F	17	A 25,400, 5/13/36 R 206,400, 5/26/36	A White cells 5,600, slight leukopenia, aspiration of sternal marrow showed very active regeneration of platelets R White cells 6,800	None			None		No
	13	M	65	A 10,500, 8/15/36 R 103,500, 8/19/36	White cells 5,600, 8/19/36	None		6 days	None	1 tablet August 11 and 1 on August 13	No
	14	F	26	A Very few platelets seen on smear 1/22/36 R Platelets appear normal on smear 4 days after taking 1 tablet, 1/26/36	A White cells 5,500	None		3 days	Sangostop (a vitamin O preparation) by mouth and injection, without result, drug stopped, immediate improvement	1 tablet each evening for several months	No
A Vogt ²¹ (1935)	15	M	63	A Complete disappearance of platelets				3 days	2 roentgen ray exposures	Took drug without symptoms for 1½ years, then 2 tablets in 5 months' interval, each produced an attack of purpura	No
	16	F	70	A 10 hours after sedormid complete disappearance of platelets R 325,000				3 days	2 roentgen ray treatments	Took sedormid 1 month without symptoms report states small dose caused attack	No
Landau ^{2k} (1936)	17			Details of case lacking				About 3 days			No
Bons and Liff ²¹ (1936)	18	F	47	A 70,000 R 190,000	Biopsy of sternal marrow showed normal marrow 10½ days after onset of acute attack, slight anemia, monocytes 7.8% A White cells 10,400 White cells 20,000	Fats caused discomfort in gastrointestinal tract		6 days	None	1 month previously, attack after 1 tablet, 1 tablet 2 successive nights before present attack	Yes
Peck and his associates ^{2m} (1936)	19	F	63	A 20,000 R 6 days after attack 260,000				Immediate when drug was stopped	None	Sedormid for 1 month previous to admission to hospital, amount not stated	No
	20	F	48					Recovered with removal of drug	None		Yes
	21	F	?	No details					None		No

TABLE 1—Cases of Purpura Haemorrhagica Due to Sedormid in the Literature from 1933 to 1938—Continued

Author	Case	Sex	Age	No of Platelets A Height of Attack R After Recovery	100,000s on Blood Cells Other Than Platelets	Previous Allergy or Purpura	Approximate Time for Recovery	Treatment	Amount of Sedormid Taken Before Purpura Appeared	Attacks Reproduced Experimentally or Accidentally
	22	M	32	A 12/16/35, 2,000 R 12/18/35, 20,000 12/19/35, 40,000 12/20/35, 70,000 12/23/35, 260,000			6 days	None		No
Metzger and Stone ²¹ (1936)	23	F	67	A 40,000 R After 6 days 300,000 R After 12 days 465,000	White cells 6,300	None	12 days	Röntgen therapy	10 tablets during 9 day interval	Yes
van Andel and Groen ²² (1937)	24	F	60	A 242,000 R 9,000 R 146,000	White cells 10,900	Bleeding from gums	3 weeks	None	5 tablets during 9 day interval	No
	25	M	43	A 9,000 R 146,000				Calcium gluconate	Drug taken at intervals for 3 months then attack after 1 tablet	No
	26	F	32	A Marked reduction in platelets			2 weeks	Oleum by mouth, redoxon (vitamin C, tablet form), fruit juices	2 tablets each night for 2 3 years, last dose (2 tablets) night before being seen by author	14 days after recovery took 1 tablet on 2 successive evenings with return of purpura
Kramer ²³ (1937)	27	M	54	A Occasional platelet						Yes
Lieberherr ²⁴ (1937)	28	F	65	1 A 23,000, 2/22 R 310,000, 3/9	1 White cells 4,900 polymorphonuclears 69.6% slight anemia and leukopenia sternal puncture, megakaryocytes 1%	None	17 days	Liver extract, 5 cc daily for 6 days, redoxon (vitamin C) 100 mg intravenously, 12 daily doses, 4 doses evening second day	1 tablet, initial dose	
	29	F	45	2 A 5,700, 9/2 R 320,000, 9/23 A 37,000, 3/12/35 9,000, 3/18/35 R 200,000, 4/9/35 405,000, 5/27/35	Anisocytosis of platelets some size of a red cell White cells 7,500, 3/13/35 monocytes 8%		27 days	Redoxon, 100 mg intravenously, 4 doses liver extract, 1 injections	40 tablets taken over an interval of 6 7 months	No

Hoffman and his associates ²¹ (1935)	30	I	7	A 55,000 R Stated to have been normal	White cells 5,200, eosinophils 0.5%	No family or personal history of allergy	3 days	None	1 tablet 4 or 5 times over period of several months before attack. 1 tablet at night before each of 3 attacks.	No
	31	I	37	A 152,000 R	White cells 9,350 neutrophils show moderate toxic granulation, some shift to left		Purpuric fading in 3 days	None	About 50 tablets past 3 years, none for several weeks, then 1/2 tablet night before attack	Yes
Moody ²² (1933)	32	M	76	A 40,000 R 239,000	White cells 9,100 5/10/37	Glyphoid vaccine for arthritis	12 days	None	2 tablets 2 days apart	Yes
	33	F	60	A 16,354, 2/12/37 R 378,000, 3/1/37	White cells 7,000, polymorphonuclears 70% anemina		18 days	Moccasin snake venom	6 tablets over period of 1 year	No
	34	F	45	No counts made			5 days		20 tablets over 2 weeks' time	No
Torrens ²³ (1928)	35		Middle age	A 80 (?) per eu mm	Anemia, red cells 50% of normal		Recovery rapid when drug was stopped	None except high calcium diet	1 tablet every night for 1 to 3 months	No
	36		Middle age				Recovery rapid when drug was stopped	High calcium diet	1 tablet every night for 1 to 3 weeks	No
Lockes ²⁴ (1928)	37	M	43	A 13,600 A 800 per eu mm 8 days after first count			10 days	None	Sedormid regularly over long periods	No
Hill ²⁵ (1934)	38	I	70	R 334,000 A 180,000			10 days		In June 1936 some tablets taken, November 1936 1 each night for about 1 week before attack	No
Napack ²⁶ (1936)	39	I	44	No details given			Prompt recovery after stopping drug		For several weeks, one tablet at night	No
2 cases										

in the platelet counts or any diminution in the total number of white cells or granulocytes, as reported by Squier and Madison³ in their studies on sensitivity to aminopyrine

On June 27 the blood count showed 11.78 Gm (86 per cent) of hemoglobin, 4,560,000 red blood cells and 9,600 white blood cells. The differential count showed 71 per cent neutrophils, 15 per cent lymphocytes, 9 per cent eosinophils, 1 per cent basophils, 4 per cent monocytes and 0.4 per cent reticulocytes.

The pressure cuff applied to the right arm at a pressure of 76 mm of mercury for five minutes caused no petechiae to appear.



Fig 2—Results of the Dalldorf capillary fragility tests during the patient's first stay in the hospital. The more distinct hemorrhagic areas represent — 20 cm pressure.

On June 28 at 9:10 a.m. $\frac{1}{2}$ tablet of sedormid was administered. At 12 o'clock noon, the platelet count was 310,000 per cubic millimeter, but by 5:30 p.m. the count had dropped to 100,000.

On June 29 the platelet count was 110,000 per cubic millimeter. The patient was given 2 sedormid tablets at 10 a.m. The platelet count at 11:15 a.m. was 120,000.

3 Squier, T. L., and Madison, F. W. Primary Granulocytopenia Due to Hypersensitivity to Amidopyrine, *J. Allergy* 6:9 (Nov) 1934.

but by 5 p m it had fallen to 40,000. The pressure test on June 29 at 10 a m, with 84 mm of mercury pressure for five minutes, showed many petechiae below the cuff. At 5 p m of the same day application of the Dalldorf instrument to the upper part of the right arm caused showers of petechiae with —20 cm pressure, scattered showers of petechiae with —15 cm pressure, 8 to 9 petechiae with —10 cm pressure. On the same day petechiae appeared over the posterior axillary folds and on the buttocks.

From June 29 until July 5 eight more observations were made with the Dalldorf instrument, using each arm alternately. The readings did not vary significantly from the previous ones until July 4 and 5, on which days the readings at —15 and —10 cm pressure showed a somewhat lessened number of petechiae to the field, probably indicating the beginning of a lessened capillary fragility.

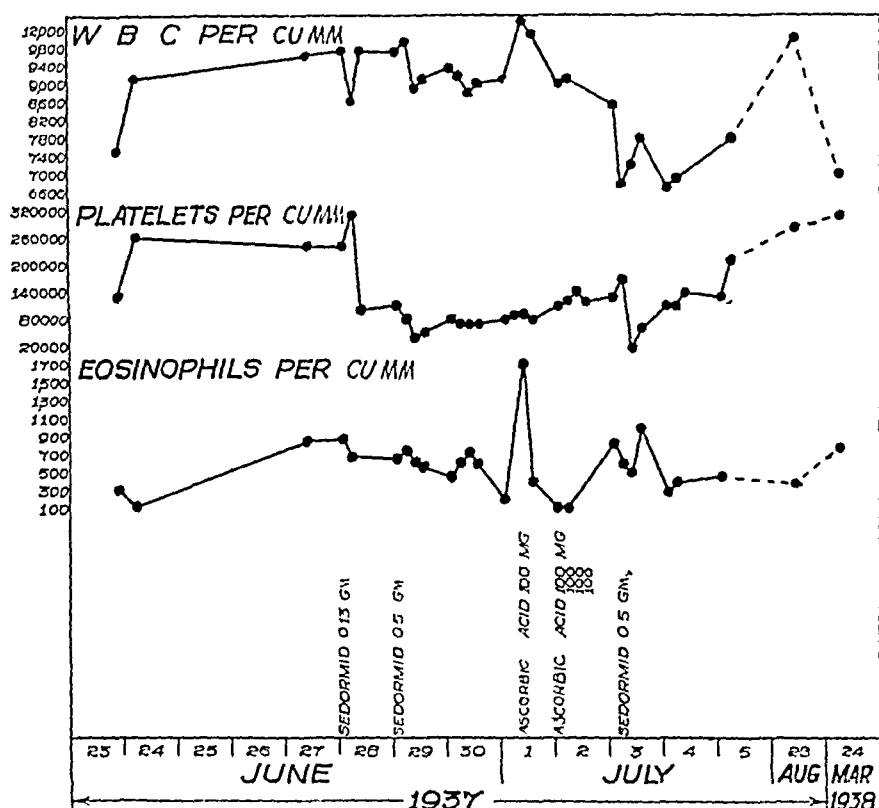


Fig 3—Correlation of platelet level and white blood cell and eosinophil counts

on July 4. This test is undoubtedly a fairly delicate quantitative test of increased capillary fragility and has value in a situation such as this, in which we were interested in determining the time required for the capillaries to recover resistance under therapy with vitamin C (ascorbic acid) (fig 2).

On June 30 the platelet counts varied from 70,000 to 90,000. Petechiae appeared over the chest, arms and neck.

On July 1 the platelets varied between 80,000 and 90,000. At 8 a m 100 mg of ascorbic acid was administered intravenously and the dose was repeated four times during the day, at intervals of four hours. At 9 p m there was an epistaxis of 4 to 5 cc. On July 2 the platelets rose to 140,000. There were two slight epistaxes during the day. The ascorbic acid content of the plasma was 1.09 mg per hundred cubic centimeters.

On July 6 the patient was discharged from the hospital, at her request, but she promised to return later for further studies. The platelet count was 210,000 on July 6, and the purpuric lesions of the skin had nearly disappeared.

Our diagnosis was purpura haemorrhagica due to the ingestion of sedormid. The chart giving results of detailed daily studies of the blood has not been included, as the values for the red cells and hemoglobin remained fairly constant, showing a slight increase, undoubtedly due to iron therapy while in the hospital. The number of red blood cells ranged from 4,550,000 on June 23 (on admission) to 5,060,000 on July 5 (at discharge), and the hemoglobin, from 11.78 Gm (86 per cent) to 12.88 Gm (94 per cent). The red cell counts were made with certified blood counting pipets (United States Bureau of Standards), and the hemoglobin estimations were made by the acid hematin method (Sahli hemoglobinometer). The Rees and Ecker method was used for the platelet counts. Figure 3 shows the correlation of platelet, white cells and eosinophil counts. This graph does not show the type of hematologic response described by Squier and Madison⁴ as characteristic of thrombopenic purpura due to food allergy. In their reported cases, the ingestion of foods to which the patients were allergic caused an immediate sharp rise in eosinophils accompanied by a drop in the platelet and white cell counts. In our blood studies on this patient, no evidence of leukopenia or granulocytopenia, described as occurring after ingestion of aminopyrine, was noted in the daily white blood cell counts.

On Aug. 28, 1937, the patient reported for a blood count, which showed 5,100,000 red blood cells, 12.33 Gm (90 per cent) of hemoglobin, 10,300 white blood cells, 49 neutrophils, 3 eosinophils, 1 basophil, 39 lymphocytes and 7 monocytes. The platelets numbered 280,000.

She reported again on March 24, 1938, at which time the blood showed 4,010,000 red blood cells, 11.5 Gm (84 per cent) of hemoglobin, 7,900 white blood cells, 45 neutrophils, 10 eosinophils, 1 basophil, 35 lymphocytes and 9 monocytes. The platelets numbered 330,000.

Approximately one year after her first admission to the hospital, on July 7, 1938, the patient returned for further experimental study.

An outline of our plans for further investigation included (1) determination of the degree of the patient's sensitivity to sedormid, (2) observation of the rate of recovery from thrombocytopenic purpura induced by ingestion of sedormid after cessation of use of the drug and without specific administration of vitamin C, (3) aspiration and study of the marrow of the sternum before and during her experimentally induced attack of purpura and (4) tests of capillary fragility (Daldorf method), to observe whether or not capillaries require a longer period for recovery of tone after an experimental attack of purpura when no vitamin C is administered (except that included in the regular hospital diet).

During the second experiment, no orange juice or lemon juice was supplied with the patient's hospital diet, but other fruit juices and vegetables were part of her regular daily meals.

Table 2 shows the amount of sedormid administered. During the period between 8 a. m. on July 7 and 7:30 p. m. on July 14, 1938, 11½ tablets, or 28.75 Gm., of sedormid were given.

Capillary fragility tests (Daldorf) before sedormid was administered on July 7 showed 20 petechiae with —20 cm. pressure and 6 to 10 petechiae

4 Squier, T. L., and Madison, F. W. The Hematologic Response in Food Allergy Eosinophilia in the Leucopenic Index, *J. Allergy* 8:250 (March) 1937, Thrombocytopenic Purpura Due to Food Allergy, *ibid.* 8:143 (Jan.) 1937.

with —15 and —10 cm pressure. Five and one-half hours after $\frac{1}{2}$ tablet of sedormid was given (4 p. m., July 7), there was a slight increase in capillary fragility. By July 13 the increase was pronounced (fig. 4). By July 19 capillary fragility tests showed a relatively normal state. These tests corresponded rather closely to the degree of capillary fragility present during her attacks in 1937 (experimental and initial). The petechiae in the area where the Dalldorf instrument was applied were larger and more distinct during this second attack (fig. 4), when no specific vitamin C was administered. It will be noted in table 2 that, after the administration of the first $\frac{1}{2}$ tablet of sedormid on

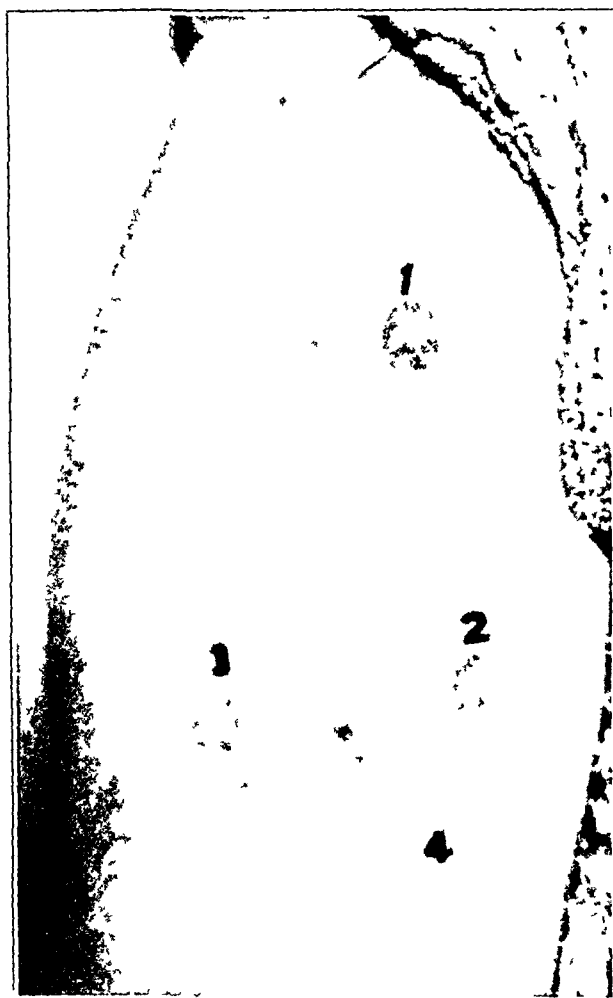


Fig. 4—Results of the Dalldorf capillary fragility tests during the patient's second stay in the hospital. 1, with—20 cm pressure, 2, with —15 cm pressure, 3, with —10 cm pressure, and 4, with —5 cm pressure.

July 7, the number of platelets decreased gradually to 80,000 per cubic millimeter on July 13, when petechiae began to appear over the chest, neck and arms. By July 15 the entire body was covered with small purpuric spots, and on July 16 there appeared ecchymotic areas about 3 to 4 cm in diameter over the anterior aspect of the upper part of the right thigh, the right shoulder and the front and back of the chest. The morphologic character of the platelets, as noted on the blood films, was not remarkable, but with reduction of platelets the films showed many small, dark, ragged disks. When the platelet count fell to 80,000 per cubic

TABLE 2—Record of Experimental Attack of Purpura Haemorrhagica Induced During Second Stay in Hospital¹

Patient—M G	Date, 1938	Dose of Sedormid	Time	Red Blood Cells, Millions	Hemo globin		Platelets	White Blood Cells	Polymorphonuclears					Lympho cytes	Eosino phils, per Cu Mm	Comment		
					%	Gm			Neutrophils			Baso- phils	Large				Small	Mono cytes
									Fila mented	Nonfla- mented	sino phils							
7/7	½ tablet, 11 30 a m		8 00	5 11	86	11 8	340,000	8,600	40	2	8	2	4	0	8	688	Plasma vitamin C, 0.67 mg per 100 cc	
			1 30			310,000	11,700	50	3	7		3	2	8	819			
			2 30			390,000	9,100	56	3	7		3	0	4	637			
			3 30			290,000	7,000	50	7	7		3	0	6	490			
			4 30			260,000	8,100	53	4	11		2	2	10	891			
7/8	1 tablet, 10 a m		6 00				230,000	10,800	58	4	5	1	2	5	7	540		
			8 00	5 08	86	300,000	9,000	41	6	5		3	8	10	450			
			12 00			190,000	7,800	51	10	6		3	0	3	468			
			1 00			210,000	7,600	50	5	11		2	8	6	886			
			2 00			200,000	8,900	54	10	8	1	2	2	5	712			
7/9	1 tablet, 11 a m		4 00				210,000	8,600	45	5	7		4	0	3	602		
			6 00			210,000	9,300	46	8	5		3	5	6	465			
			8 00	5 16	86	230,000	7,500	40	5	10		3	4	11	750			
			1 00			180,000	9,100	62	4	6		2	2	6	546			
			3 00			170,000	8,900	38	2	10		4	4	6	890			
7/10	2 tablets, 8 45 a m		5 00				180,000	8,100	42	3	11	1	3	8	6	891		
			8 00	5 32	86	210,000	8,500	43	6	7		3	6	8	595			
			10 45			200,000	9,050	40	7	6		4	2	5	543			
			1 00			150,000	8,850	15	1	4		4	4	6	354			
			3 00			170,000	8,600	48	4	8		3	6	4	688			
7/11	2 tablets, 9 30 a m		5 00				150,000	8,100	40	4	6		4	2	8	593		
			8 00	5 22	86	160,000	9,300	44	4	6		4	0	6	606			
			8 00			180,000	10,100	44	4	6		4	0	6				
			11 30			230,000	8,700	43	8	6		3	3	10	522			
			2 00			210,000	8,900	48	3	6		3	7	6	534			
7/12	2 tablets, 9 a m		4 00				160,000	8,700	44	7	6		4	0	3	522		
			6 00			150,000	9,100	36	4	5	1	4	8	6	455			
			8 00			160,000	8,800											
			8 00	5 11	86	130,000	9,200	38	6	6	1	3	9	10	552			
															Plasma vitamin C, 1.11 mg per 100 cc			

7/15	11 00 1 00 3 00 5 00 8 00	130,000 130,000 130,000 110,000 100,000	9,700 8,000 8,300 8,050 7,100	42 ¹ 36 53 42 23	12 6 3 12 18	6 12 7 6 6	3 4 3 3 3	0 0 1 2 4	10 6 6 8 14	592 1,086 591 483 426	Plasma vitamin C, 1 32 mg per 100 cc
7/14	11 00 2 00 4 00 6 00 8 30	100,000 80,000 80,000 80,000 80,000	7,050 7,300 7,700 7,500 6,700	46 46 32 34 40	14 6 10 6 4	6 7 9 8 10	2 3 4 4 3	6 2 2 0 7	8 8 7 11 9	423 511 693 600 670	Plasma vitamin C, 1 05 mg per 100 cc
7/17	11 00 1 00 3 00 7 20 8 30	80,000 80,000 80,000 80,000 65,000	7,000 6,700 7,300 10,100 7,900	40 40 36 32 46	10 9 4 8 0	6 4 7 4 7	4 3 4 4 3	0 4 7 2 7	4 13 6 12 10	420 263 511 404 553	Bleeding time, 2 min Coagulation time, 4 min Clot retraction good Bleeding time, 2 min
7/10	11 00 1 00 5 00 8 00	70,000 70,000 70,000 55,000	7,700 8,900 7,100 6,100	52 53 38 36	4 4 4 4	6 4 9 8	3 3 3 4	6 5 2 6	2 4 16 4	462 376 639 512	Clotting time, 6 min No clot retraction
7/17	10 30 12 30 2 30 5 00 12 00	63,500 70,000 75,000 73,000 130,000	6,700 6,400 6,500 6,700 8,050	42 44 44 48 48	6 6 4 6 6	7 4 5 8 8	3 3 3 3 2	8 6 8 8 4	6 10 9 9 14	469 512 325 614 614	Plasma vitamin C, 1 20 mg per 100 cc
7/18	7 00 8 30	140,000 190,000	8,200 8,300	60 60	10 10	6 6	1 1	7 7	6 6	492 492	Plasma vitamin C, 1 20 mg per 100 cc
7/19	1 00 5 00 8 30	200,000 290,000 320,000	8,600 8,300 6,900	56 56 56	8 8 8	5 5 5	2 2 2	7 7 7	4 4 4	490 490 490	Plasma vitamin C, 1 20 mg per 100 cc
7/25	7 18	460,000	7,900	56	8	5	2	7	4	490	Plasma vitamin C, 1 20 mg per 100 cc

* Note time required for return to the normal platelet level when no vitamin O therapy was used

millimeter or below, larger forms appeared. Some were about one half the size of a red blood cell. As the platelet count rose, after cessation of administration of sedormid, there appeared to be a tendency for aggregation of platelets on the films.

On July 7 before any sedormid was given, aspiration of the marrow of the sternum was performed. This procedure was repeated on July 15, when the platelet count was 70,000 per cubic millimeter, and after several purpuric spots had appeared in the skin over various portions of the body. The results were

	July 7	July 15
Myeloblast	5	5
Promyelocyte	1	1
Myelocytic neutrophil	12	12
Myelocytic eosinophil	3	6
Metamyelocytic neutrophil	23	17
Metamyelocytic eosinophil	3	7
Polymorphonuclear neutrophil	22	18
Polymorphonuclear eosinophil	4	2
Lymphocyte	3	4
Megakaryocyte	1	3
Proerythroblast	4	9
Erythroblast (including normoblast)	19	16

On July 15 the platelets in the marrow films were markedly reduced in number and tended to be larger than normal (4 to 6 microns in diameter).

Table 2 shows that no parallel increase in the number of eosinophils accompanied leukopenia and a drop in the number of platelets, which has been said to occur in food allergy, and there was no leukopenia with granulocytopenia, which has been stated to occur in persons sensitive to aminopyrine and allied drugs. This table does show an average rise above normal in the number of eosinophils (also shown in fig. 3), which we attributed to the allergic state causing the attacks of asthma and hay fever.

It will be noted that the percentage of vitamin C in the blood plasma of the patient was slightly lower on July 8, 1938 than on June 21, 1937, at the time of her first entry. The values for vitamin C in the plasma gradually rose during the time of the second experiment (July 7 to 19, 1938). This occurred in the absence of parenteral or oral administration of vitamin C other than that included in her diet. We are unable to interpret the significance of this rising percentage of vitamin C in the plasma during the second experiment, unless the low amount 0.67 mg per hundred cubic centimeters, on admission (July 8) was the result of a diet inadequate in vitamin C before the patient came to the hospital.

SUMMARY

No definite evidence was found that vitamin C by either oral or parenteral administration, diminished the intensity of the purpuric lesions and hemorrhagic manifestations of the patient reported, nor did it shorten the period necessary for recovery from these manifestations.

This patient was apparently only slightly sensitive to sedormid and was less sensitive after the lapse of a year, during which time she had not taken any sedormid. Differential cell counts and study of the marrow of the sternum, both before and after the induced attack of purpura, showed stimulation of the early granulocyte elements, i. e.,

myeloblasts, myelocytes and metamyelocytes. The erythroid elements were increased, probably as part of a stimulation of granulocytes and erythropoietic elements. The megakaryocytes were not increased in either of the two counts.

The formed elements of the peripheral blood other than the platelets showed very slight, if any, change during either experiment. We have a careful record of daily blood counts during the entire period of the experiments, but did not include all of them because of a desire to conserve space.

AN EPIDEMIC DISEASE OF THE RESPIRATORY TRACT

HOBART A REIMANN, M D

AND

W PAUL HAVENS, M D

PHILADELPHIA

In the past few years numerous clinicians have described isolated cases and epidemics of infection of the respiratory tract especially associated with pulmonary involvement. The disease in most instances resembled epidemic influenza so closely that clinical differentiation could not be made, and in only one or two studies were attempts made to differentiate the disease from influenza by serologic or other laboratory methods. Definite diagnoses in this group of infections of the respiratory tract cannot be made, of course, until the etiologic agents in the different diseases become known.

Various names have been given to the diseases described, such as acute pneumonitis,¹ acute influenza pneumonitis,² acute interstitial pneumonitis,³ atypical pneumonia,⁴ bronchopneumonia,⁵ pseudolobar-bronchopneumonia,⁶ benign circumscribed pneumonia,⁷ disseminated focal pneumonia,⁸ acute diffuse bronchiolitis⁹ and capillary pneumonia

From the Department of Medicine, Jefferson Medical College Hospital

Presented in part with Dr Joseph Stokes Jr before the Association of American Physicians, Atlantic City, N J, May 2, 1939

1 Allen, W H. Acute Pneumonitis, *Ann Int Med* **10** 441-446 (Oct) 1936. Rainey, W G, and Burbidge, J R. Acute Pneumonitis or Atypical Pneumonia, *Journal-Lancet* **59** 101-104 (March) 1939.

2 Bowen, A. Acute Influenza Pneumonitis, *Am J Roentgenol* **34** 168-174 (Aug) 1935.

3 Smiley, D F, Showacre, E D, Lee, W F, and Ferris, A W. Acute Interstitial Pneumonitis. A New Disease Entity, *J A M A* **112** 1901-1904 (May 13) 1939.

4 Cass, J W. The Question of "Influenza" and Atypical Pneumonia, *New England J Med* **214** 187-193 (Jan 30) 1936.

5 Miller, F N, and Hayes, M G. Bronchopneumonia of Mild Severity at the University of Oregon, *Northwest Med* **38** 12-14 (Jan) 1939.

6 Jeanneret, R, and Fame, F. L'image radiologique de la bronchopneumonie grippale, *Rev med de la Suisse Rom* **51** 418-422 (June 10) 1931.

7 Ramsay, H, and Scadding, J G. Benign Broncho-Pulmonary Inflammations Associated with Transient Radiographic Shadows, *Quart J Med* **32** 79-95 (April) 1939.

8 Scadding, J G. Disseminated Focal Pneumonia, *Brit M J* **2** 956-959 (Nov 13) 1937.

9 McKinlay, C A. Acute Diffuse Bronchiolitis, with Report of a Case, *Journal-Lancet* **59** 90-91 (March) 1939.

These terms may be fairly descriptive of the underlying pathoanatomic changes, but beyond this they serve no useful purpose. Furthermore, in our recent experience with a disease to be described, all of these terms were too restrictive, since they are applicable only in the minority of cases of the severe form with pneumonia in an epidemic in which the lungs were seldom involved (fig 2).

In the spring months of 1938, 8 cases of a severe form of atypical pneumonia were studied at the Jefferson Medical College Hospital¹⁰. Several more occurred among the hospital personnel in August, November and December. During this time the number of cases of mild infection of the respiratory tract was not unusual, and in only 1 instance did it appear to be related to the severe form. Because of the peculiar nature of the disease, attempts were made to determine the etiologic agent¹¹. From 2 patients a filtrable infectious agent was recovered which when inoculated into animals caused bacteria-free pneumonia, characterized by an inflammatory reaction of the interstitial tissue of the lungs with a mononuclear cell exudate and often encephalitis. Unfortunately, the agent disappeared during passage in animals, and proof of its etiologic relationship to the disease was not established. Nevertheless, because of this suggestive evidence and the clinical resemblance of the disease to other known virus infections of the respiratory tract, it was suggested that a virus was the cause.

During the same season of 1938 many sporadic cases and epidemics of disease strikingly like the one described here were observed in Ohio, Delaware, Oregon, New York, Minnesota, Missouri¹² and elsewhere, giving reason to believe that a special infectious agent was common to all.

EPIDEMIC OF 1939

Sporadic cases of an unusual form of pneumonia were observed in the Jefferson Hospital, as stated, until late in 1938, but in January 1939 an epidemic of a mild disease of the respiratory tract began in Philadelphia, which reached widespread proportions in February¹³. In our experience it was the most widespread epidemic of many years.

10 Reimann, H. A. An Acute Infection of the Respiratory Tract with Atypical Pneumonia. A Disease Entity Probably Caused by a Filtrable Virus, *J A M A* **111** 2377-2384 (Dec 24) 1938.

11 Stokes, J., Kenney, A. S., and Shaw, D. R. A New Filtrable Agent Associated with Respiratory Infections, *Tr Coll Physicians Philadelphia* **6**:329-333, 1939.

12 Miller, M. E., Wingfield, P. B., Harrington, F. E., Langmuir, A. D., and Edwards, J. C. Personal communication to the authors.

13 Reimann, H. A., and Stokes, J., Jr. An Epidemic Infection of the Respiratory Tract in 1938-1939. *Tr A Am Physicians* **54**:123-129, 1939.

Similar outbreaks, with a high morbidity rate, were reported from New York, Minnesota, Illinois, England,¹⁴ France and elsewhere at about the same time. In some places schools were closed in an effort to stop the spread of the disease, and other localities were apparently not affected at all. Since most patients were not ill enough to seek medical aid, it was impossible to learn the real extent of the pandemic, so that its incidence is not accurately reflected in the statistics of city and state health departments. Furthermore, the mild form may be confused with true influenza or similar infections, and the severe form with pneumonia may be mistaken for the pneumonias of bacterial origin.

It would be important to know whether the disease observed in 1938 was caused by the same agent as that of 1939. There is reason to believe that it was, because of the clinical similarity of both the mild and the severe type in the two outbreaks, but many more cases of the mild than of the severe form occurred in 1939. This behavior is similar to that of epidemic influenza in 1918-1919. Numerous isolated cases of a severe infection of the respiratory tract occurred a year or two before the outbreak of the great pandemic.¹⁵

CLINICAL STUDIES

Since it was thought that a study of the epidemic in a more or less "closed" and easily controlled group of persons would be of value in describing the disease, our observations were limited chiefly to the interns, nurses and medical students comprising a group of 813 persons at Jefferson Medical College and Hospital. Of this group, 407 persons, or 50 per cent, were ill presumably of the same disease. Of the 407 persons affected, only about 100 were ill enough to be admitted to the hospital for treatment. The date of onset of the illness in these patients is shown in figure 1.

It was not possible to measure the period of incubation because of the numerous possibilities of exposure. We believe the incubation period was short, perhaps one or two days, but others have suggested it to be two weeks.

The disease was primarily an inflammation of the mucous membranes of the respiratory tract, usually of the nose, pharynx and larynx, occasionally including the trachea and bronchi, and in a few cases the bronchioles and lungs. Constitutional symptoms were usually in proportion to the extent and intensity of the mucosal inflammation. The

14 Andrewes, C. H. Epidemic Influenza, *Lancet* **1** 589-590 (March 11) 1939.

15 Hammond, J. A. B., Rolland, W., and Shore, T. H. G. Purulent Bronchitis, *Lancet* **2** 41-45 (July 14) 1917. Abrahams, A., Hallows, N. F., Eyre, J. W. H., and French, H. Purulent Bronchitis. Its Influenzal and Pneumococcal Bacteriology, *ibid* **2** 377-382 (Sept. 8) 1917.

clinical course was remarkably uniform in most cases, differing chiefly in degree of severity. For simplicity in discussion, the cases were classified as those of mild (ambulatory patients), moderately severe (bedfast patients) and severe forms.

Mild Form—By far the largest proportion of the 407 patients (307, or 75 per cent) were ambulatory. Their illnesses perhaps would

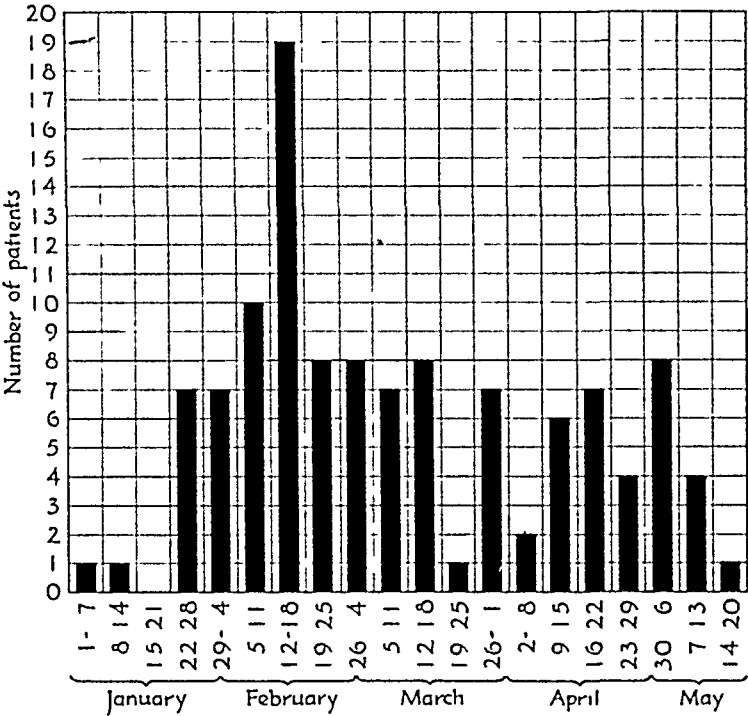


Fig 1—Weekly incidence of cases of the moderately severe and severe form in the epidemic

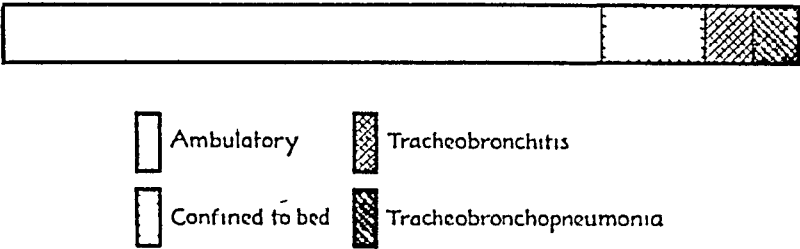


Fig 2—Relative proportion of ambulatory patients (75 per cent) and patients confined to bed (25 per cent). Twelve per cent of all patients had tracheobronchitis, and 6 per cent had pneumonia.

ordinarily be regarded as unimportant “colds,” but because of the coincidence with other more severe, but clinically similar, infections, we have regarded them as part of an epidemic of a single disease entity (fig 2). These persons usually complained of coryza, obstruction of the nose, malaise, frontal headache, weakness, dizziness, sweating and anorexia. Rhinorrhea and lacrimation were rare, but the conjunctivas

were often injected. There was occasional dry cough, but rarely fever. The illness lasted from one to several days. A number of persons had one or two relapses, which in some cases were severe.

Moderately Severe and Severe Forms—About 100, or 25 per cent, of those who were sick had to go to bed. Of this number, 25 had tracheobronchitis and 25 had tracheobronchopneumonia. The onset in most cases (97 per cent), as in those of the mild form, was insidious. Headache, dry or mild sore throat, coryza, malaise, muscular pains, cough and shivering were the most frequent complaints, in the order named. In a day, or after several days, these symptoms increased in severity. Aching, backache, frontal headache, pain in the eyeballs, photophobia, malaise and sweating were present in over 80 per cent of cases. Over 70 per cent of patients had persistent hacking or paroxysmal cough, which often interfered with sleep. Only 27, however, raised sputum, but never more than 30 cc a day. Sixty patients complained of dry, raw or sore throat, and hoarseness with aphonia developed in 4. A few patients with intensely inflamed throats were surprisingly free from local discomfort. Catarrhal or exudative symptoms were rare. Of the abdominal symptoms, anorexia (52 cases) and muscular soreness from coughing (16 cases) were most frequent. Vomiting and diarrhea were present in 12 instances.

The severity of the illness was generally in proportion to the extent and intensity of the inflammation of the mucous membranes. Most of the severely ill patients had evidence of tracheobronchitis or pneumonia, but a few without pulmonary invasion felt worse than those with it, but for a shorter time. Hoarseness and aphonia were more common in those with pulmonary invasion, as were drenching sweats and weakness. Fever lasted on an average two and a half days in patients without involvement of the lungs, four and six-tenths days in those with tracheobronchitis and eight and two-tenths days in those with pneumonia.

Physical Signs—The patients often looked ill, the face was flushed, and the eyes were reddened. The most constant feature of the moderately severe form (92 per cent of cases) was the inflamed mucous membranes of the upper portion of the respiratory tract. According to Dr. Calvin Fox, who examined each of these patients, the mucous membranes, particularly the lymphoid tissue, of the nose, oropharynx and pharynx, and frequently the larynx, including the epiglottis, arytenoid cartilages and vestibule, and the trachea were intensely red and dry, with varying degrees of congestion. Occasionally the congestion in the nose was sufficient to obstruct breathing. In the severely sick patients, crusting with excoriations resembling pinpoint hemorrhages were observed on the nasal septum. In a few cases the vocal cords were inflamed and thickened. Little or no exudate was found in the nose,

but small quantities of tenacious mucopus were sometimes present in the oropharynx. Cervical lymphadenopathy was rarely observed.

The severe cough of most patients suggested tracheal, bronchial or pulmonary involvement, but in only 4 patients with tracheobronchitis who did not have frank pneumonia were rales or suppressed breath sounds heard in the hilar areas of the lungs. In 23 of 86 cases roentgenograms made by Dr. Karl Kornblum showed evidence of tracheobronchitis (fig. 3) in the absence of physical signs, a fact emphasized by others (Scadding).⁸ Three patients were regarded as having tracheobronchitis in the absence of roentgenographic evidence because of rales in the interscapular areas. Evidence of pneumonia was present as indicated by abnormal physical signs and roentgenographic findings in 25 patients. The roentgenographic features will be the subject of a separate paper.

The temperature was usually elevated and averaged from 38.3 to 39.5 C (101 to 103 F), and the pulse rate was increased in proportion

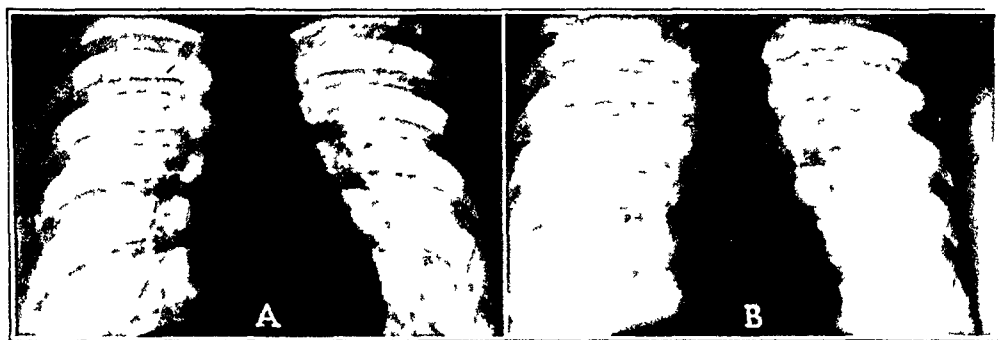


Fig. 3—Roentgenograms in a case of tracheobronchitis. The patient had been ill for three days with symptoms of the moderately severe form with nasopharyngitis. There was little cough or sputum and no abnormal physical signs in the lungs. *A*, made during the illness, shows generalized increase in the pulmonary markings in both lungs, indicating acute tracheobronchitis; in *B*, made five days later, the shadows are less prominent.

to between 110 and 120. The respiratory rate was occasionally increased. The clinical record in a typical case is given in figure 4. The sputum, when present, was occasionally blood tinged, but otherwise was not characteristic. The number of leukocytes in the blood ranged between 5,000 and 8,000 per cubic millimeter, often with a slight increase in the proportion of polymorphonuclear cells. The sedimentation rate of the erythrocytes was usually increased.

Patients with Pneumonia—Pneumonia developed in 25 patients. There were 8 cases of pneumonia among 38 interns. The onset was usually insidious, like that already described, but signs of spread to the lungs appeared after several days or a week or more had elapsed. In

several cases signs of pneumonia were present in the first few days. The clinical picture in general was similar to that described before,¹⁰ and need not be given in detail again. Outstanding features were nasopharyngolaryngitis, tracheitis and bronchitis of varying degrees of extent and severity, paroxysmal cough, minimal amounts of exudate and sputum, frontal headache, aching of the eyes, photophobia, slight cyanosis, dyspnea, and frequently profuse sweating. There were occasional dulness and suppressed breath sounds, invariably rales were present in one or both interscapular areas, but sometimes were confined to one lobe, or were heard in several lobes at the same time or in succession. Weak bronchophony or egophony was occasionally heard. Roentgenograms almost always showed localized or diffuse areas of

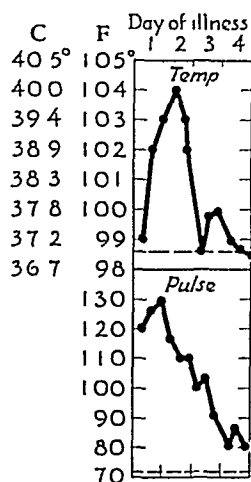


Fig 4—Temperature and pulse rate in a case of moderately severe respiratory infection with nasopharyngotracheobronchitis in a nurse aged 20. She felt well until February 9, when onset occurred with malaise, chilliness, fever, sweating, headache, backache, aching of the eyeballs and a dry, harsh, nonproductive cough. Some soreness and pain in the left axilla were noted. The patient was hoarse, her face was flushed, and the eyes were reddened. The mucosa of the nose and throat was swollen, dry and reddened. The lymph follicles in the pharynx were particularly inflamed and swollen, and the visible blood vessels were distended. The chest was normal except for suppressed breath sounds in the lower lobe of the right lung posteriorly, a roentgenogram showed generalized increase in the pulmonary markings, particularly in both hili. The leukocyte count was 5,000. Cultures made of the pharyngeal exudate showed *Str viridans* in predominance, *Str haemolyticus*, *N catarrhalis*, *Staphylococcus albus* and diphtheroids. General aching of the limbs, nausea and vomiting occurred on the second day, but convalescence thereafter was rapid.

density where abnormal signs were found (fig 5). In 3 cases shadows of pulmonary invasion were present without physical signs, and in 4 cases physical signs were present without shadows in the roentgenograms.

Relative bradycardia was noted only in the cases of severe disease with pneumonia of long duration. Fever was continuously high or occasionally remittent, and the temperature declined by lysis (fig 6). The disease with pneumonia lasted from two to seventeen days, with an average of eight and two-tenths days. Often there was loss of weight of 5 to 10 Kg (11 to 22 pounds). All the patients recovered. Convalescence was usually rapid, but was prolonged in several cases by weakness and sweating. In a number of cases relapse, with mild nasopharyngitis, occurred after several weeks. The number of leukocytes was usually normal or slightly increased toward the end of the illness. The sedimentation rate of the erythrocytes was increased especially late in the disease. All cultures of the blood were sterile. In similar cases in New York city, Chickering¹⁶ noted a marked increase in the number of mononuclear cells in the sputum.

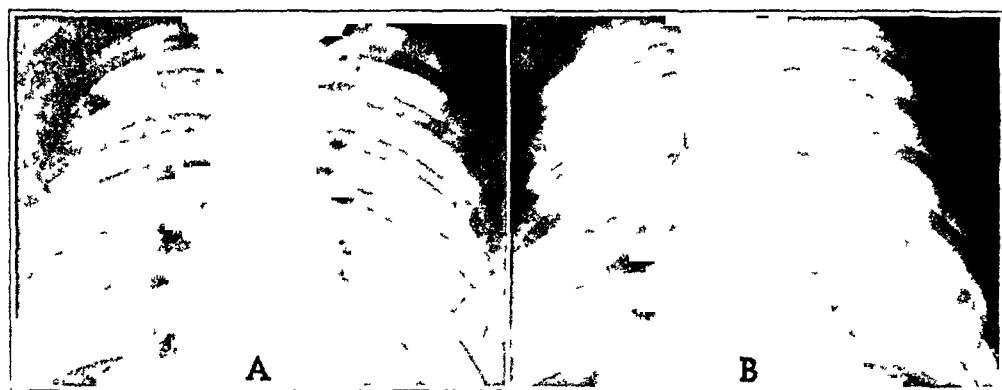


Fig 5—Roentgenograms in a case of tracheobronchopneumonia charts for which appear in figure 6. *A*, taken on the second day of the disease shows intensification of hilar shadows, especially on the right. *B*, taken on the eighth day, shows a diffuse, mottled shadow in the middle and lower lobes of the right lung. On the thirteenth day a faint shadow appeared in the hilar area of the lower lobe of the left lung.

OTHER MANIFESTATIONS

As in many other infectious diseases, we believe that in some instances organs and tissues other than the respiratory tract may be affected. In 1938 the cases of 2 patients with symptoms of encephalitis were mentioned¹⁰. In the group studied in 1939 4 persons had many of the typical signs and symptoms described, but were much more troubled by general abdominal cramps, watery diarrhea, anorexia, nausea and vomiting. The illness lasted several days in each case, left the patient weak and caused the loss of from 2 to 5 Kg (5 to 10 pounds) in weight.

¹⁶ Chickering. Personal communication to the authors.

In 3 medical students whose signs and symptoms warranted inclusion of their cases in the epidemic, jaundice developed five to seven days after the beginning of the symptoms of nasopharyngitis. The clinical course was then typical of the disease commonly known as catarrhal jaundice. Whether this syndrome and gastroenteritis were both caused by the same infectious agent is of course uncertain, but since no similar conditions developed in the group studied either before or after the epidemic they were presumably a part of the disease.

Relapse or recrudescence of the disease occurred in 17 patients of the group. Relapses were more severe than the preceding attack in some and less severe in others. Here, again, it is uncertain whether relapses

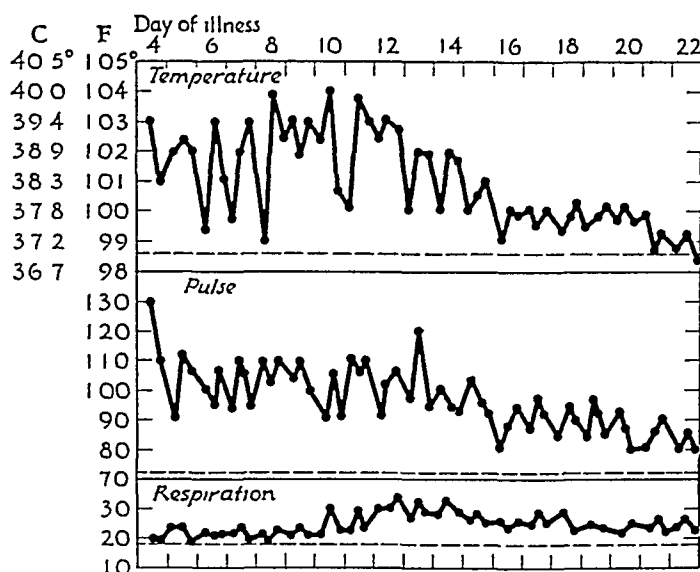


Fig 6—Severe infection of the respiratory tract with nasopharyngotracheo-bronchopneumonia in an intern aged 25, who had had a slight cold with obstruction of the nose and injection of the conjunctivas for several days. On January 24, a rather abrupt onset of dry, wracking cough, substernal soreness, malaise, general aching, photophobia, chilly sensations, fever and sweating was noted. The nasopharynx was inflamed. The leukocyte count was 8,600. Ferrets were inoculated with nasopharyngeal washings on January 24. Two days later the patient's throat was sore, and hoarseness developed. There was slight suppression of breath sounds in the base of the right lung posteriorly, and rales were heard the next day. Herpes appeared on the lips, and paroxysms of cough were severe. Several days later dyspnea and cyanosis required oxygen for relief. The respiratory rate was not greatly increased, in spite of dyspnea and cyanosis, which appeared about the second week. Tachycardia was present early in the course, followed by relative bradycardia. Nasopharyngitis, photophobia and sweating persisted for ten days. Rales were heard in the base of the left lung on the thirteenth day. The leukocyte count was 14,000. Rales and hoarseness persisted until the twenty-first day. Roentgenograms are shown in figure 5. Loss of weight was 8.2 Kg (18 pounds). Convalescence was slow but uneventful.

were caused by the same agent as that in the first attack, by a biologic modification of it or by a different agent, but because of similar clinical features the relapses were regarded as being due to the same cause

COMPLICATIONS

There were no important complications among our patients except gastroenteritis and jaundice, which may not be complications at all, but a part of the disease itself. In 5 cases, after several days of the mild symptoms as described, typical acute follicular tonsillitis with leukocytosis developed. A pure culture of hemolytic streptococci was recovered from the exudate on the tonsils. Maxillary sinusitis developed in 2 cases. In several patients not included in the group studied, but admitted to the general medical service of the hospital, typical lobar pneumonia caused by pneumococci of types I, II and VII developed after an illness of several days or a week with nasopharyngotracheitis, presumably of the kind described here.

ETIOLOGIC STUDIES

As in the previous year, when a filtrable agent was recovered from 2 patients,¹¹ anesthetized ferrets were inoculated intranasally by Dr. Joseph Stokes Jr and Miss Shaw with nasopharyngeal secretions taken from 11 patients early in the course of the disease. Aside from demonstrating the absence of the virus of epidemic influenza, no decisive results were obtained. In a few instances the animals appeared to be ill after inoculation, but on further passage no evidence of disease developed. Complement fixation tests with influenza virus as antigen made on the blood of 15 patients gave negative results.

Bacteriologic studies of sputum and nasopharyngeal exudates showed the presence of *Streptococcus viridans*, *Streptococcus haemolyticus*, *Neisseria catarrhalis*, diphtheroids and staphylococci, named in the order of frequency. None was considered to be of etiologic importance. *Bacillus influenza* was not encountered. There was also a remarkable scarcity of pneumococci. They were recovered in only 6 cases, usually from the sputum and rarely from pharyngeal swabs, which had to be made in most cases because of the absence of sputum. Exudate was routinely injected into mice, but only pneumococci of types IV, VIII, XVIII and XXIX and two unclassified strains were isolated. They were not regarded as etiologically significant.

TREATMENT

No active treatment was used in cases of the mild form. Patients were advised to remain in bed, but seldom did so. Patients with moderately severe attacks went to bed. They were usually kept isolated in

separate rooms. Headache and aching were controlled with codeine sulfate, 0.03 to 0.06 Gm ($\frac{1}{2}$ to 1 grain) by mouth, as needed. An ice cap to the head was often comforting. Acetylsalicylic acid, acetophenetidin and aminopyrine were seldom used because of the diaphoresis they cause, which in many cases was an annoying symptom of the disease itself. Cough was often relieved by menthol cough lozenges or by steam from a water vaporizer. For severe cough codeine was given to permit sleep. Pain in the abdominal muscles from coughing was relieved by a snugly fitting binder. Oxygen was helpful only when dyspnea and cyanosis were present. The bowels were kept open with mild laxatives and enemas as needed, and the diet was unrestricted except for patients with nausea, vomiting or diarrhea.

Swabs and applications to the mucous membranes of the nose and throat were found to cause discomfort and were generally not used. A spray of physiologic solution of sodium chloride or a weak solution of sodium perborate as a gargle often relieved the sense of dryness in the nose and throat. An aqueous spray containing a 1 per cent solution of ephedrine hydrochloride or epinephrine hydrochloride was used to relieve nasal obstruction.

The question of chemotherapy and specific antipneumococcus serum therapy was raised in several of our cases in which pneumococci were present in the sputum, but not in the blood. In a few cases, in spite of the atypical nature of the pneumonia, both sulfapyridine and serum were given, but the absence of a prompt response suggested that the pneumococci present had no etiologic significance. Sulfapyridine given alone to certain patients had no beneficial effect and usually caused discomfort, with nausea and cyanosis. Several patients in the general medical service of the hospital in whom typical pneumonia due to *Pneumococcus* types I, II and VII subsequently developed, were promptly benefited by sulfapyridine and specific antipneumococcus serum.

COMMENT

The epidemic disease of the respiratory tract reported was considered to be an etiologic entity clinically similar to epidemic influenza, but caused by a different agent. The disease occurred in varying degrees of severity, from the mildest forms with inflammation of the nose and throat, of a few days' duration, to the severe forms with pulmonary involvement, often lasting several weeks. Cases of the mild form far outnumbered those of the severe form, and for this reason we believe it to be misleading to apply restrictive names indicating special forms of bronchiolitis or pneumonia to cases of the severe form alone, as many have done. It should be recognized that, as in the case of influenza, both mild and severe forms may be due to

the same cause without the agency of bacteria, although bacteria may eventually invade the damaged lung¹⁷ From the standpoint of public health mild infections are all potentially dangerous They may be the precursors of an outbreak of a more serious epidemic disease of the respiratory tract caused by the invasion of bacteria, like that which occurred in 1918-1919 after influenza Fortunately, in the winter of 1939 either the mild disease did not favor bacterial invasion or highly invasive organisms, such as pneumococci, hemolytic streptococci, staphylococci or Pfeiffer's bacilli, were not as prevalent as usual, and the mortality rate in our group of patients was nil

*Differential Diagnosis of the Philadelphia Epidemic of 1939, Epidemic Influenza and Febrile Catarrhs**

	Epidemic Influenza	Febrile Catarrhs	Philadelphia Epidemic of 1939
Onset	Sudden	Insidious	Insidious
Symptoms	Constitutional symptoms preponderant	Respiratory symptoms preponderant	Constitutional symptoms preponderant
Cough	Short and dry	Paroxysmal, irritating, painful, often productive	Paroxysmal, hacking, nonproductive
Voice	Husky	Hoarse	Husky or hoarse
Throat	Posterior pharyngitis no exudate	Tonsillitis as well as pharyngitis, exudate common	Nasopharyngolaryngitis, no exudate
Fever	Sometimes diphasic	Rarely diphasic	Rarely diphasic
Complications	Bronchiolitis and pneumonia	Bronchitis or bronchopneumonia	Tracheobronchopneumonia considered part of the disease, not a complication
Epidemic	Short, with rapid "peaking"	Prolonged and "grumbling"	Prolonged
Contacts	Clinical picture uniform, although graded in severity	Clinical picture variable with frank tonsillitis in contacts	Clinical picture uniform, although graded in severity
Leukocyte count	Not diagnostic	Not diagnostic	Not diagnostic
Virus	Influenza virus recoverable from pharynx	Influenza virus not concerned	Influenza virus not concerned

* The differentiation was based on the criteria of Stuart Harris and his associates¹⁸

It is interesting to apply to the disease described the clinical criteria proposed by English observers for the differentiation of epidemic influenza from the "febrile catarrhs"¹⁸ In general the disease we describe fits more closely the pattern of influenza, yet certain important differences exist as shown in the accompanying table, chief of which are the absence of the virus of influenza, the insidious onset, the paroxysmal

17 Scadding, J. G. Lung Changes in Influenza, *Quart J Med* 6 425-465 (Oct) 1937

18 Stuart-Harris, C. H., Andrewes, C. H., Smith, W., Chalmers, D. K. M., Cowen, E. G. H., and Hughes, D. L. A Study of Epidemic Influenza, with Special Reference to the 1936-1937 Epidemic, Medical Research Council Special Report Series, no 228 London His Majesty's Stationery Office, 1938

cough, sweating and the epidemiologic features. The disease differs from the febrile catarrhs chiefly in the constitutional symptoms, the paucity of exudate and the uniform clinical picture.

It is probable that the disease is the same as, or similar to, that described by other investigators in 1938-1939, but one cannot assume its identity with the forms described in previous years without further evidence, since few attempts at differentiation with biologic methods were made. In some of these cases the disease may have been true influenza, and in some, other entities. It is probable that a group of numerous infections may cause disease of the respiratory tract of which the present one is a member. Only by the perfection of methods of identifying the causative agents can they finally be separated into specific entities.

Diagnosis in cases with the form of pneumonia described here is not difficult when many cases occur in an epidemic of similar infections, both of the mild and the severe type. Isolated cases may be difficult to recognize, and in our first experiences¹⁰ psittacosis, typhoid fever and pulmonary tuberculosis were often considered. The possibility of secondary bacterial invasion and pneumonia caused by the ordinary varieties of bacteria must always be kept in mind.

The disease should perhaps be given a temporary general name, such as grip (as dissociated from true influenza), until the etiologic agent is discovered. Many features of the disease, such as its epidemiology, the close resemblance to other diseases known to be caused by filtrable viruses, the normal leukocyte count and the absence of evident causative bacteria, suggest to us that a filtrable virus is the cause, but proof is wanting.

SUMMARY

An epidemic disease of the respiratory tract occurred in Philadelphia and elsewhere in the winter of 1939. Reports of similar outbreaks in many parts of this country and in Europe suggest that it may have been pandemic. Of a group of 813 persons in the personnel of the Jefferson Medical College and Hospital, 50 per cent were ill. The majority of patients (88 per cent) were ill with nasopharyngolaryngitis. Six per cent had tracheobronchitis in addition, and 6 per cent had tracheobronchopneumonia. In most of the severely ill patients the lungs were presumably involved by the infectious agent suspected, without the agency of the usual varieties of bacteria. There were no serious complications, and all the patients recovered. The disease resembles epidemic influenza in many respects, but it is caused by a different agent. It represents a clinical entity probably caused by a filtrable virus.

EFFECT OF RENAL RETENTION OF VITAMIN C ON SATURATION TESTS

A FORMULA FOR COMPENSATION OF THIS FACTOR OF ERROR

JOHN B LUDDEN, M D

AND

IRVING WRIGHT, M D

NEW YORK

In 1933, Harris, Ray and Ward¹ demonstrated the excretion of vitamin C in the urine and established a relationship between the excretion and the intake of this vitamin. Since that time, a number of chemical methods for the determination of the state of vitamin C nutrition in man have been presented. The determination of the twenty-four hour "resting level" of urinary excretion presented many technical disadvantages and was impractical in the study of ambulatory patients. The content of ascorbic acid in the fasting blood was observed to vary considerably with the recent dietary intake of vitamin C and gave only a rough index of the actual state of saturation.² The test dose method, in which a given dose of ascorbic acid is administered and the output in the urine is used as an index of saturation, was found to have many advantages. Oral test doses of 300 to 1,000 mg were first used.³ The

From the Department of Medicine of the New York Post-Graduate Medical School and Hospital

This study was aided by a grant from Merck & Co, Inc, Rahway, N J, who also furnished the ascorbic acid used

1 Harris, L J, Ray, S N, and Ward, A. The Excretion of Vitamin C in Human Urine and Its Dependence on the Dietary Intake, *Biochem J* **27**:2011, 1933

2 (a) Wright, I S. The Present Status of the Clinical Use of Cevitamic Acid (Ascorbic Acid) (Crystalline Vitamin C), *Am J M Sc* **192** 719, 1936 (b) Greenberg, L D, Rinehardt, J F, and Phatak, N M. Studies on Reduced Ascorbic Acid Content of the Blood Plasma, *Proc Soc Exper Biol & Med* **35** 135, 1936 (c) Portney, B, and Wilkinson, J E. Vitamin C Deficiency in Peptic Ulceration and Hematemesis, *Brit M J* **1** 554, 1938

3 (a) Johnson, S W, and Zilvd, S S. Urinary Excretion of Ascorbic and Dehydro-Ascorbic Acids in Man, *Biochem J* **28** 1393, 1934 (b) Abbasy, M A, Harris, L J, Ray, S N, and Marrack, J R. Diagnosis of Vitamin-C Subnutrition by Urine Analysis. Quantitative Data—Experiments on Control Subjects, *Lancet* **2**:1399, 1935 (c) Youmans, J B, Corlette, M B, Akeroyd, J H, and Frank, H. Studies of Vitamin C Excretion and Saturation, *Am J M Sc* **191**:319, 1936 (d) Harris, L J, Abbasy, M A, and Yudkin, J. Vitamins in Human Nutrition. Vitamin C Reserves of Subjects of the Voluntary Hospital Class, *Lancet* **1** 1488, 1936 (e) Goldsmith, G A, and Ellinger, G F. Ascorbic Acid in Blood and Urine After Oral Administration of a Test Dose of Vitamin C Saturation Test, *Arch Int Med* **63**:531 (March) 1939

large factor of error due to the variability of absorption and utilization from the gastrointestinal tract was eliminated by the intravenous administration of the test doses.⁴ A five hour test, after the intravenous injection of 1 Gm of ascorbic acid, was proposed by Wright, Lilienfeld and MacLenathen^{4a}, they observed that at least 500 mg was normally excreted in the first twenty-four hours, 75 per cent or more of it during the first five hours. Tests using smaller doses (for example, 100 mg) are subject to the criticism that moderate changes in the immediately previous vitamin C intake or metabolism may produce proportionately greater changes in the results without indicating the true saturation state. It has been stated that *all* vitamin C in the blood above a certain level spills over into the urine. That this is not true is demonstrated by the fact that as little as 36 mg has been collected after a 1,000 mg test dose. In most instances the five hour test has been highly satisfactory, but it was first observed in this laboratory⁵ that a delay in the excretion of vitamin C occurred in some patients with impairment of renal function. Sendroy and Miller⁶ have recently presented similar observations. Thus, erroneous low values may be observed when single urine specimens obtained three, five, six or eight hours after any test dose of whatever size, are used as criteria of the state of vitamin C nutrition. As would be expected, the levels of vitamin C in the blood under such conditions are found to remain high for longer periods than are normal after the ingestion of the vitamin. Hence, determinations on the blood may give false impressions as to the degree of saturation. In the present investigation the vitamin C content of urine and blood plasma was studied during a twenty-four hour period following an intravenous test dose of 1 Gm of ascorbic acid. Subjects with and without evidence of renal insufficiency were studied in an effort to evaluate the error due to variations of renal function.

4 (a) Wright, I. S., Lilienfeld, A., and MacLenathen, E. Determination of Vitamin C Saturation—A Five Hour Test After an Intravenous Test Dose, *Arch Int Med* **60** 264 (Aug.) 1937. (b) Hawley, E. E., and Stephan, D. J. Rate of Urinary Excretion of Test Doses of Ascorbic Acid, *Proc Soc Exper Biol & Med* **34** 854, 1936. (c) Ralli, E. P., Friedman, G. J., and Kaslow, M. An Excretory Test for Vitamin C Deficiency and Subnutrition, *Proc Soc Exper Biol & Med* **36** 52, 1937. (d) Finkle, P. Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, *J Clin Investigation* **16** 587, 1937. (e) Faulkner, J. M., and Taylor, F. H. L. Observations on the Renal Threshold for Ascorbic Acid in Urine, *ibid* **17** 69, 1938.

5 (a) Wright, I. S., and MacLenathen, E. Vitamin C Saturation—Kidney Retention After Intravenous Test Dose of Ascorbic Acid, *Proc Soc Exper Biol & Med* **38** 55, 1938. (b) Wright, I. S. Cevitamic Acid (Ascorbic Acid, Crystalline Vitamin C). A Critical Analysis of Its Use in Clinical Medicine, *Ann Int Med* **12** 516, 1938.

6 Sendroy, J., Jr., and Miller, B. J. Renal Function as a Factor in the Urinary Excretion of Ascorbic Acid, *J Clin Investigation* **18** 135, 1939.

METHOD

Each subject was placed on a diet containing a minimum of vitamin C (less than 15 mg daily) for at least twelve hours preceding the test and for the twenty-four hours after the administration of the test dose. At 9 o'clock on the morning of the test the patient voided, 6 cc of blood was drawn for plasma analysis and 1 Gm of ascorbic acid, dissolved in 10 cc of physiologic solution of sodium chloride, was injected intravenously. Complete specimens of urine were obtained exactly one and one-half, three and five hours after the injection, and were titrated immediately. The remaining (nineteen hour) specimen was collected in tightly stoppered dark brown bottles, which contained sufficient glacial acetic acid to bring the pH to 3, and kept at ice box temperature. This specimen was titrated immediately after the last micturition. For a number of the patients with normal vitamin C excretion and for all the patients with delayed excretion, the specimen obtained on the twenty-fourth hour was collected and titrated apart from the rest of the nineteen hour specimen, blood was obtained from these patients at periods corresponding with the urine collections, and the plasma was analyzed for vitamin C.

The vitamin C in the urine was determined by a modification of Tillman's 2, 6-dichlorophenolindophenol method⁷ and in the plasma by the sodium tungstate precipitation method of Farmer and Abt⁸ (Duplicate plasma determinations using the metaphosphoric acid technic of Farmer and Abt⁹ gave values that agreed within 0.04 mg per hundred cubic centimeters.) In every instance the plasma analysis was done within thirty minutes after venipuncture, and suitable blanks were used in all titrations. Potassium cyanide was not used as a preservative, since previous studies in our own and other laboratories¹⁰ have shown that it reduces the dye and produces erroneous values.

RESULTS

In normal saturated subjects the vitamin C level in the plasma reached a high peak about two minutes after the injection (chart 1), it fell rapidly during the first hour and one-half and then gradually returned to a point slightly above the control level at the end of twenty-four hours (chart 2). The rate of urinary excretion of vitamin C

7 Tillmans, J., Hirsch, P., and Jackisch, J. Das Reduktionsvermögen pflanzlicher Lebensmittel und seine Beziehung zum Vitamin C. Der Gehalt der verschiedenen Obst- und Gemüsearten an reduzierendem Stoff, *Ztschr f Untersuch d Lebensmitt* **63** 241, 1932.

8 Farmer, C. J., and Abt, A. Ascorbic Acid Content of the Blood, *Proc Soc Exper Biol & Med* **32** 1625, 1935.

9 Farmer, C. J., and Abt, A. Determination of Reduced Ascorbic Acid in Small Amounts of Blood, *Proc Soc Exper Biol & Med* **34** 146, 1936.

10 (a) Wright, I. S., and MacLenathan, E. Potassium Cyanide as an Agent Inhibiting the Oxidation of Vitamin C in Vitro, *J Lab & Clin Med* **24** 808, 1939. (b) Friedman, G. J., Rubin, S. H., and Kees, W. Effect of Addition of KCN to Whole Blood on Indophenol-Reducing Power of Plasma, *Proc Soc Exper Biol & Med* **38** 358, 1938. (c) Farmer, C., and Abt, A. Invalidation of Plasma Ascorbic Acid Values by Use of Potassium Cyanide, *ibid* **38** 399, 1938. (d) Cushman, M., and Butler, A. M. Use of Cyanide in the Determination of Ascorbic Acid, *ibid* **39** 534, 1938.

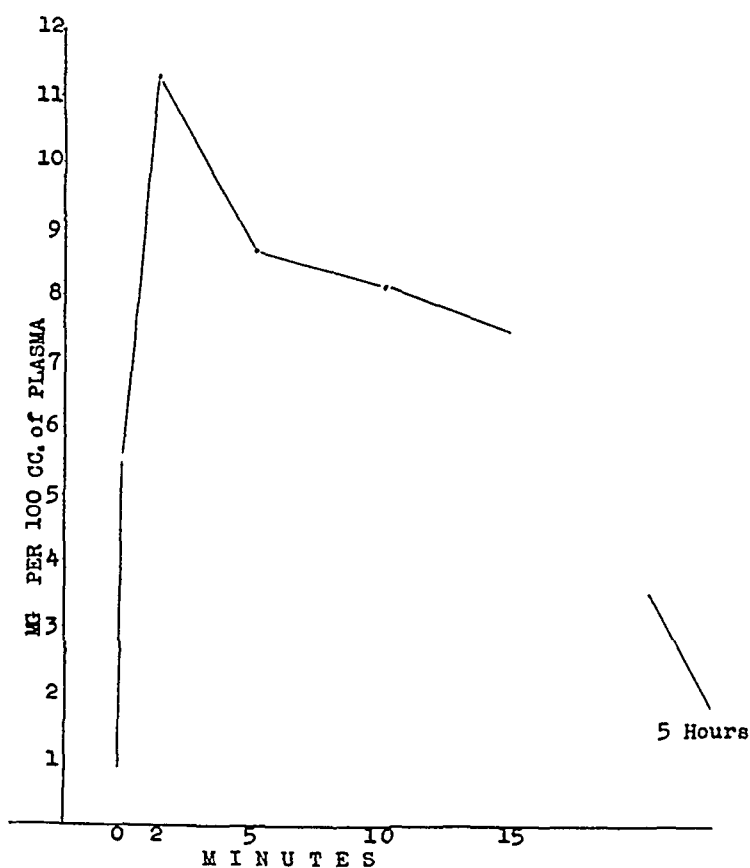


Chart 1—Vitamin C curve for plasma of a normal subject after intravenous injection of 1 Gm of ascorbic acid The five hour output in the urine was 549 mg

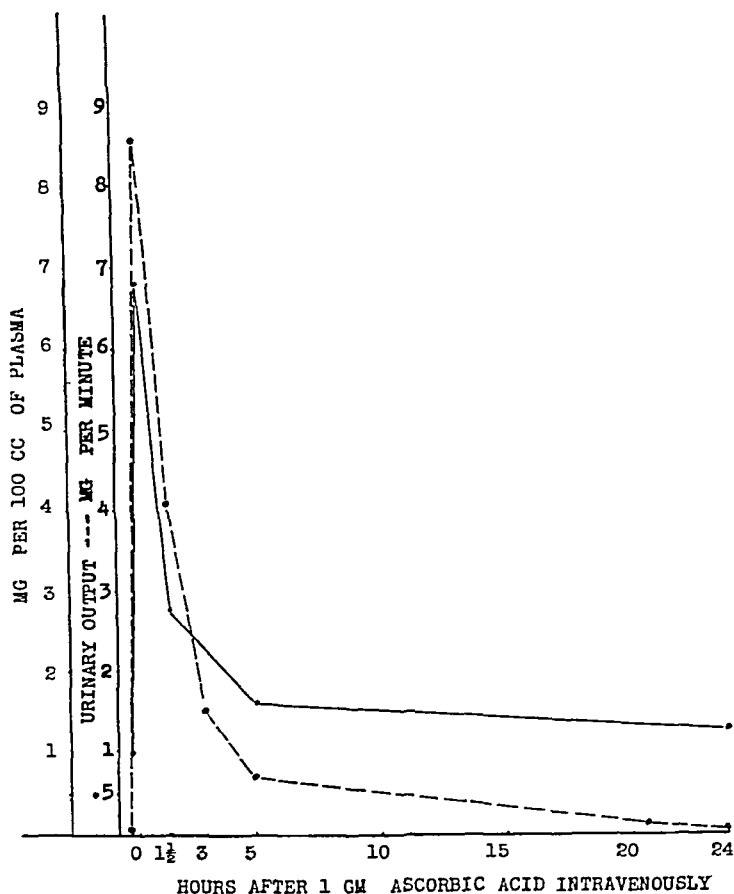


Chart 2—Typical curves for vitamin C in the urine and plasma of a normal subject, urine, o---o, plasma, ●—● The total excretion in one and one-half hours was 432.9 mg, in five hours, 661.1 mg, in twenty-four hours, 788.2 mg

showed a definite relation to the level in the plasma, it was highest during the first fifteen minutes and remained relatively high during the first hour and one-half, although the fall was rapid until the fifth hour. By this time 75 per cent or more of the total twenty-four hour output had been excreted. The excretion rate had returned to slightly above the control level at the end of twenty-four hours.

In patients with impaired excretion of vitamin C and normal saturation, urinary excretion of vitamin C was slow when compared with the concentration in the plasma. For both urine and plasma, the return

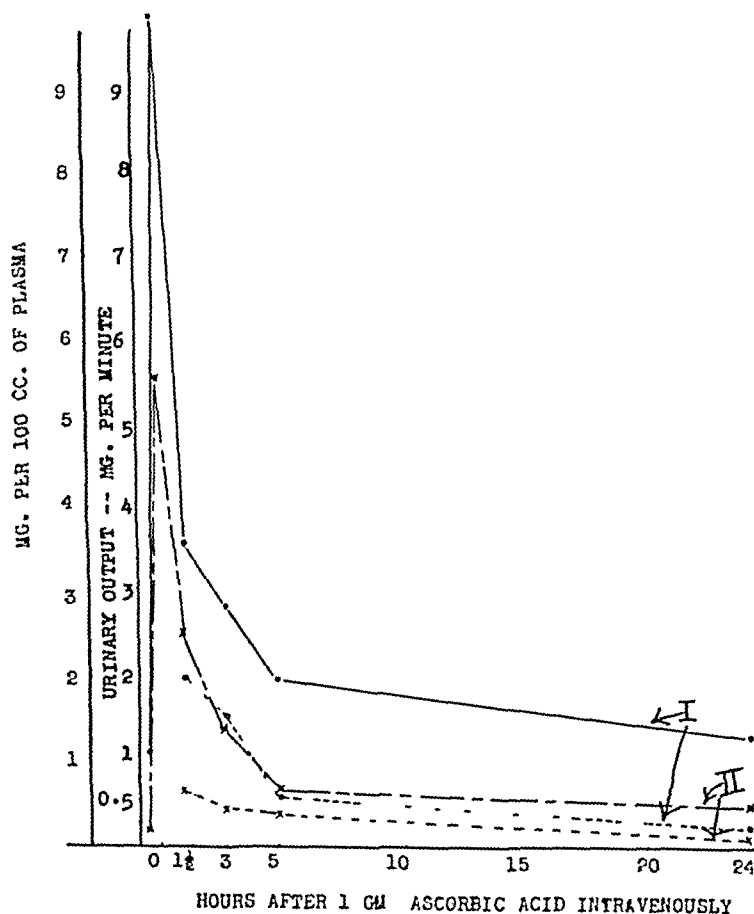


Chart 3—Vitamin C in the urine and plasma of patients with delayed urinary excretion of the vitamin. Patient I had normal, and patient II had deficient, vitamin C nutrition. Urine, I, o-----o, II, x---x, plasma I, ●—●, II, λ-----λ. The total excretion of vitamin C, in milligrams, was as follows:

	I	II
After one and one-half hours	178.2	53.5
After five hours	380.1	143.6
After twenty-four hours	602.4	237.1

toward control levels was delayed for varying periods. In patients with impaired excretion, but in an unsaturated state of vitamin C nutrition, the vitamin C content of the plasma dropped normally although that of the urine showed evidence of impaired excretion (chart 3). The urine

appeared to give more reliable evidence of the renal function in regard to vitamin C than the plasma

The significant data for 8 patients with evidence of impaired vitamin C excretion are presented in Table 1, together with the results of other laboratory studies pertaining to renal function. The impairments of excretion in patients J K, J M and F M were discovered in the course of routine studies and there was no other evidence to suggest renal insufficiency, these patients were all men over 65 years of age with

TABLE 1—Results for Patients with Impaired Vitamin C Excretion

Patient	Age	Diagnosis	Vitamin C				Blood			Urine		
			Control Plasma Mg per 100 Cc	3 Hour Urine, Mg *	24 Hour Urine, Mg *	5/24 Hr Excr, %†	Nonprotein Nitrogen	Urea Nitrogen	Urea Clearance % of Norm U	Specific Gravity	Protein	Rbc /H P F
JK	80	Arteriosclerosis	0.35	380	602	63	29	14	104	1.020	0	0
JM	69	Arteriosclerosis	1.03	306	845‡	60	40	13	76	1.012	0	0
FM	67	Arteriosclerosis	0.16	143	237	60	24	13	135	1.020	Tr	1
MB	45	Malignant hypertension	0.1	179	271	66	29	16	62	1.008§ 1.012	2+	13
SB	25	Malignant hypertension	0.59	139	257	54	55	23	29	1.006§ 1.018	3+	3
MF	23	Chr glomerulonephritis	0.49	240	444	54	54	43	31	1.009§ 1.015	2+	1
JP	42	Chr pyelonephritis (in uremia)	0.34	30	83	35	125	80	11	1.004§ 1.010	1+	1
MT	17	Malignant hypertension (in uremia)	1.50	78	151‡	52	75				1+	

* After 1 Gm ascorbic acid intravenously

† Percentage of the 24 hour output excreted during the first 5 hours

‡ Computed from data of 5 hour test

§ Maximum variations during Mosenthal 2 hour test

obliterative peripheral arteriosclerosis. Patients M B, S B and M F all had other clinical and laboratory evidence of diminished renal function. (The curve of ascorbic acid excretion of patient S B is compared with that of a patient with normal renal function and a similar vitamin C deficiency in chart 4.) In all of these patients except J P and M T, who were in terminal uremia when studied, the twenty-four hour plasma and urine vitamin C levels had returned to slightly above control values. We have interpreted this as evidence that the twenty-four hour excretion was a satisfactory index of saturation except in these 2 cases of far advanced renal insufficiency. Gross errors, however, would have resulted in every case if the three or five hour output had been used as an index of saturation. The data for patient J K will illustrate the magnitude

of this error The five hour output, of 380 mg., gave evidence of a deficiency, whereas the twenty-four hour output, of 602 mg., was entirely normal

The results of twenty-four hour excretion studies of 29 subjects with a wide range of saturation levels and with various degrees of renal efficiency are presented in table 2

The proportion of the twenty-four hour output of vitamin C excreted during the first five hours after the test dose varied from 54 to 99 per cent These variations appeared to depend, to some extent, on the state of saturation, but a very important factor was the renal function in relation to vitamin C The curves for vitamin C in the urine of subjects 11, 16,

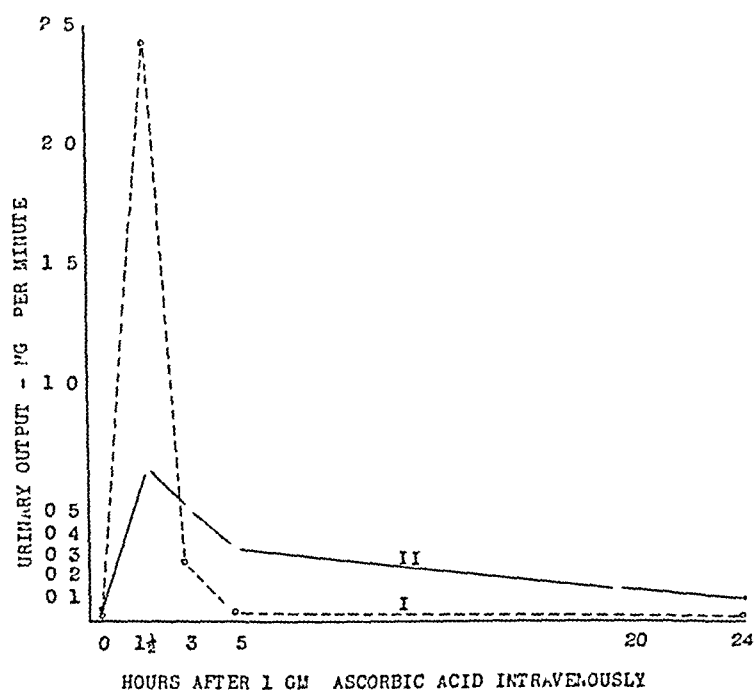


Chart 4—Comparison of excretion of vitamin C following test dose by (I) a patient with normal renal function and (II) a patient with impaired renal function, both patients having vitamin C deficiency The total excretion of the vitamin, in milligrams, was as follows

	I	II
After one and one-half hours	222	58
After five hours	247	138
After twenty-four hours	253	256

The urea clearance in patient I was 135 per cent, in patient II, 29 per cent

20, 23 and 26, indicated delayed excretion, the proportion of the twenty-four hour output excreted in the first five hours ranged from 54 to 66 per cent The curves for subjects 12 and 7 showed moderately impaired excretion; although there was no clear laboratory evidence of impaired renal function, both subjects were aged men with marked peripheral arteriosclerosis The vitamin C excretion for the remaining 22 subjects

was interpreted as being within normal limits, although the five hour output varied from 77 to 99 per cent of the twenty-four hour output. The five hour output was observed to become proportionately less in relation to the twenty-four hour output as the state of saturation improved. This observation was confirmed by tests done on patients

TABLE 2—Results of Twenty-Four Hour Vitamin C Excretion Tests After Intravenous Injection of 1 Gm of Ascorbic Acid

Subject	Vitamin C in Diet	Control Plasma, Mg per 100 Cc	Actual Urinary Output of Vitamin C					Predicted 24 Hr Output,† Mg	Percent age of Error§
			1½ Hr, Mg	5 Hr, Mg	24 Hr, Mg	1½/5 Hr Excr, %*	5/24 Hr Excr, %†		
1	Exc	0.98	432.9	661.1	788.2	65.4	83.9	779.9	1.04
2	Exc	1.17	423.0	689.4	784.8	61.3	87.8	812.0	7.26
3	Exc		359.2	603.2	757.0	59.5	79.6	747.8	1.21
4	Exc	1.32	414.0	637.0	737.6	65.0	86.3	754.2	2.25
5	Exc	1.41	377.8	618.8	732.3	61.1	84.5	757.3	3.27
6	Good	0.78	352.0	562.9	716.8	62.5	78.5	679.6	5.18
7	Good	0.95	267.1	483.4	674.8	55.2	71.6	626.8	7.10
8	Good	0.58	327.4	510.8	633.4	64.1	80.6	609.0	3.85
9	Good	0.91	313.6	522.3	624.5	60.4	83.6	644.6	3.21
10	Good	0.41	304.0	479.5	620.5	63.4	77.3	574.8	7.37
11	Good	0.95	178.2	380.1	602.4	46.8	63.1	555.6	7.76
12	Good	0.57	218.5	430.1	585.2	50.8	73.7	590.4	0.89
13	Fair	0.50	341.9	479.5	526.8	71.3	91.0	544.1	3.28
14	Fair	0.61	265.5	418.7	497.8	63.4	84.0	502.5	0.94
15	Good	0.79	266.2	418.2	481.1	63.6	86.9	500.3	4.44
Low Normal Level									
16	Fair	0.49	87.7	239.8	443.7	36.7	54.1	458.9	3.42
17	Fair	0.22	290.4	358.2	374.0	81.0	95.7	386.3	3.28
18	Poor	0.17	286.0	311.1	315.9	91.9	98.4	321.9	1.90
19	Fair	0.30	234.4	269.4	283.4	87.0	95.1	283.7	0.05
20	Fair	0.31	75.5	179.1	271.1	42.1	66.1	289.0	6.62
21	Poor	0.26	237.4	262.5	268.7	90.4	97.6	273.0	1.60
22	Fair	0.26	245.4	263.3	265.3	93.4	99.2	271.3	2.26
23	Fair	0.59	58.3	138.5	256.4	42.1	54.3	223.9	12.67
24	Fair	0.33	221.9	247.0	252.3	89.9	97.9	257.4	2.02
25	Poor	0.13	216.6	240.0	246.4	90.3	97.7	249.8	1.33
26	Poor	0.16	53.5	143.6	237.1	37.2	60.5	268.3	13.20
27	Poor	0.17	194.7	211.6	221.7	92.0	95.4	218.8	1.31
28	Poor	0.09	88.3	103.3	108.7	85.6	95.0	109.4	0.65
29	Poor	0.18	97.4	97.6	97.9	99.8	99.8	98.6	0.71
								Mean	3.12 ± 2.3

* Percentage of the 5 hour output excreted the first 1½ hours

† Percentage of the 24 hour output excreted the first 5 hours

‡ Predicted 24 hour output according to the formula in the text

§ Percentage of error of predicted 24 hour output when compared with actual 24 hour output

|| Omitted from calculation of mean due to large relative deviation

both before and after saturation, typical results of such a study may be seen in chart 5. In our experience the factor of saturation does not account for five hour excretion percentages of less than 75.

A careful study of the accumulated data revealed a definite correlation between (1) the percentage of the five hour output excreted during the first one and one-half hours and (2) the percentage of the twenty-four hour output excreted during the first five hours. Accordingly, this correlation was analyzed as follows. A graph, employing these variables,

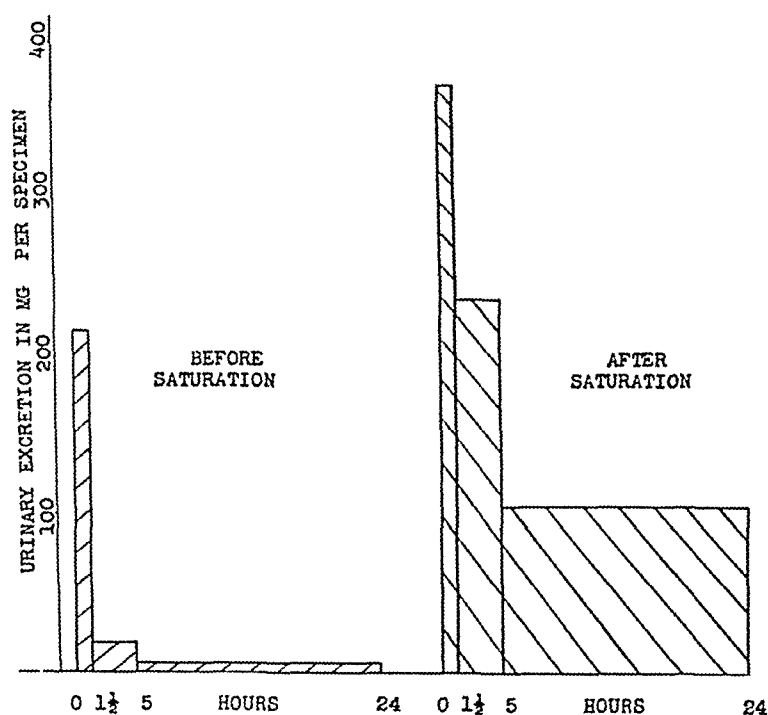


Chart 5—Effect of previous saturation on the twenty-four hour excretion of vitamin C after the intravenous injection of 1 Gm of ascorbic acid. The patient received 4,600 mg of ascorbic acid orally during the five days between tests. Before saturation, 247 mg was excreted in twenty-four hours and 240 mg (97 per cent) in the first five hours. After saturation, 732 mg was excreted in twenty-four hours and 618 mg (84 per cent) in the first five hours.

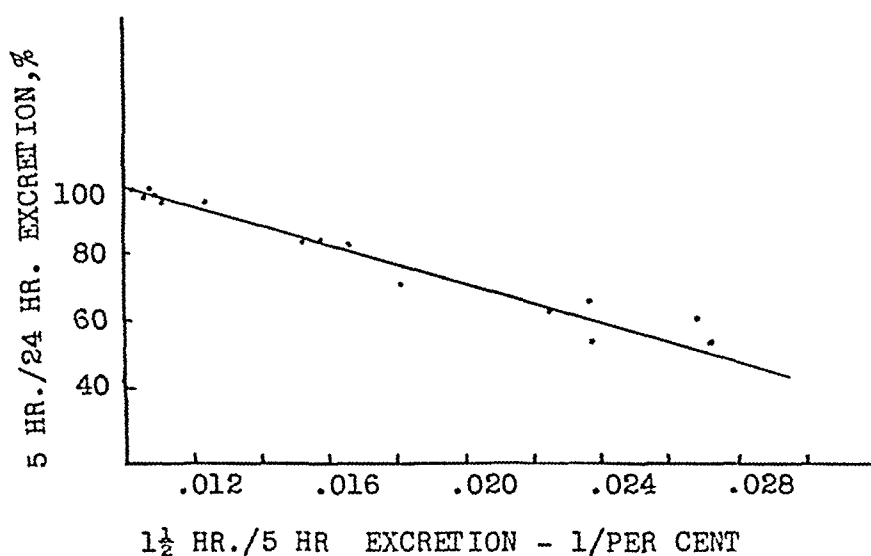


Chart 6—The percentage of the twenty-four output of vitamin C excreted during the first five hours after the test dose is plotted against the reciprocal of the percentage of the five hour output excreted in the first one and one-half hours. The line is drawn from the formula given in the text, the dots represent the experimental values.

was plotted from the tabulated data, and the shape of the resulting curve indicated an equation of the form $y = a + b/x$, with y representing the percentage of the twenty-four hour output excreted in five hours and x representing the percentage of the five hour output excreted in one and one-half hours. We set $x' = 1/x$ and calculated the values of x' . Plotting points x' and y , we found that they lay nearly on a straight line (chart 6). Values for a and b were obtained from the data by the method of averages. By simple substitution the following working formula was then developed

$$C = \frac{ab}{1.26a - 0.27b}$$

In this formula, C represents the amount of vitamin C (in milligrams) excreted in twenty-four hours, a , the amount excreted in one and one-half hours, and b , the amount excreted in five hours.

With this formula, the data for one and one-half and five hour urine specimens were sufficient to predict the actual twenty-four hour output with a mean error of 3.12 ± 2.3 per cent and a maximum error of 13 per cent. This degree of error seemed relatively insignificant when compared with the constant and possible errors of previously described urinary excretion tests.

Accordingly, we suggest the following modified technic for the original ^{4a} five hour vitamin C saturation test.

Have the patient omit breakfast on the morning of the test. Immediately after the patient has voided and discarded the preliminary urine, inject intravenously 1 Gm of ascorbic acid dissolved in 10 cc of physiologic solution of sodium chloride. Collect urine specimen 1 exactly one and one-half hours after the injection and specimen 2 exactly five hours after the injection. Titration preferably should be done immediately after each collection, but, if necessary, the first specimen may be preserved as outlined previously and titrated at the end of the test.

By means of the values obtained for specimen 1 (a) and the sum of those for specimens 1 and 2 (b), the predicted twenty-four hour excretion, C , may be calculated according to the formula $C = \frac{ab}{1.26a - 0.27b}$. The value thus calculated may be termed the *saturation index*.

COMMENT

This modification has retained all the advantages of the original five hour vitamin C saturation test ^{4a} and has compensated for the error due to variations in renal function. The only patients so far found to be unsuitable for this test were in advanced uremia. Such patients can be readily recognized and do not present problems primarily of vitamin C nutrition. Hyperavitaminosis C may be easily produced in such patients if large repeated doses are given. Parallel studies of the content in the plasma and the urine, followed by daily analyses of the plasma during vitamin C therapy, have clarified the interpretation of these rare exceptions.

These studies also appeared to confirm the observations of Van Eekelen,¹¹ Lund,¹² Faulkner and Taylor^{4e} and Ralli, Friedman and Rubin¹³ that a definite augmentation in the rate of vitamin C excretion occurred when the level in the plasma exceeded 12 to 14 mg per hundred cubic centimeters. As the values fell below this "threshold" the rate of excretion gradually decreased, although some vitamin C continued to be excreted even when the level in the plasma was very low.

Since a definite delay of vitamin C excretion was observed in several aged persons with no other evidence of renal insufficiency, the question arose whether some renal impairment existed which was not determined by the usual tests of renal function. More detailed studies and prolonged observations of such patients will be necessary for the exact evaluation of this question. At the present time, we should interpret the data as indicating impaired vitamin C excretion when the vitamin C output during the first one and one-half hours after the test dose is less than half the total five hour output. Such delayed excretion would appear to be more significant in unsaturated than in saturated persons. The use of other well established renal function tests seems indicated for such persons.

SUMMARY

A modified five hour vitamin C saturation test which compensates for the error due to variations in renal function is proposed.

Twenty-four hour studies of the urinary excretion and plasma concentration of vitamin C after an intravenous test dose of 1 Gm of ascorbic acid are reported for patients with a wide range of saturation levels and with various degrees of renal insufficiency.

Except for patients in the uremic state the twenty-four hour excretion appears to give a satisfactory index of the state of vitamin C nutrition. The excretion during shorter test periods gives false low values for patients with retarded vitamin C excretion. Patients with impaired renal excretion of vitamin C may give no other evidence of renal insufficiency.

A correlation exists between (1) the percentage of the five hour output excreted during the first one and one-half hours after the

11 Van Eekelen, M. On the Amount of Ascorbic Acid in Blood and Urine. The Daily Human Requirements for Ascorbic Acid, *Biochem J* **30** 2291, 1936.

12 Lund, H. Eine quantitative und spezifische Methode zur Ascorbinsäuretitration im Harn und zur Bestimmung des Schwellenwertes, *Klin Wchnschr* **16** 1085, 1937.

13 Ralli, E. P., Friedman, G. J., and Rubin, S. H. The Mechanism of Vitamin C Excretion in Man Studied by Simultaneous Vitamin C and Inulin Clearances, *J Clin Investigation* **17** 765, 1938.

test dose and (2) the percentage of the twenty-four hour output excreted during the first five hours. In view of this, a formula is presented by which the actual twenty-four hour output may be satisfactorily predicted through the use of data on urine specimens obtained one and one-half and five hours after the test dose.

The proposed test, in our experience, gives a more reliable estimation of the actual state of vitamin C saturation than any other method available at this time.

In addition, an estimation of the renal function for vitamin C may be obtained through the analysis of data from this test.

FEVER IN CONGESTIVE HEART FAILURE

DERA KINSEY, M D

AND

PAUL D WHITE, M D

BOSTON

It is well known that fever often occurs in patients with congestive heart failure. During the early use of the clinical thermometer Wunderlich¹ noted this finding, but he also said that subnormal temperatures were by no means uncommon.

In reviewing the medical literature it is surprising to find so little has been said either about fever in relation to congestive heart failure or concerning the frequency with which complications occur in patients suffering from that disease.

Harrison's² opinion, as expressed in his book entitled "Failure of the Circulation," is as follows.

Fever in some degree occurs in a large proportion of patients with congestive heart failure. A slight increase in temperature may possibly be dependent on the increase in the metabolic rate which many patients exhibit, but fever of more considerable magnitude usually signifies infection, infarction, or thrombus formation. More commonly fever is to be ascribed to pulmonary infection.

Cohn and Steele³ reviewed 172 cases in which symptoms or signs of heart failure were presented. In 153 of these cases there were, on two or more occasions, elevations of rectal temperature to at least 100 F. In 49 cases the occurrence of fever was without satisfactory explanation, and after completing their study the authors came to the conclusion that heart failure alone could cause fever, by interference with heat loss. In only 9 cases of their series, however, were postmortem examinations made.

PRESENT STUDY

We have reviewed the cases of 200 patients with congestive heart failure who were admitted to the Massachusetts General Hospital from 1933 to 1938. These cases include all types of cardiac disease. In every

From the Medical Clinic of the Massachusetts General Hospital.

Read at the Annual Meeting of the American Heart Association, St. Louis, May 12, 1939.

1 Wunderlich, C. R. A. On the Temperature in Diseases. A Manual of Medical Thermometry, London, New Sydenham Society, 1871, pp. 430 and 431.

2 Harrison, T. R. Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1936, p. 264.

3 Cohn, A. E., and Steele, J. M. Unexplained Fever in Heart Failure, J. Clin. Investigation **13** 853, 1934.

instance rectal temperature readings were taken ⁴ Postmortem examinations were made of 50 of the 81 patients who died in the hospital We have classified the grades of fever and of heart failure as follows

Type and Grade of Heart Failure ⁵—(1) Left ventricular failure alone—dyspnea, with or (usually) without moist rales at the bases of the lungs, accentuation of the second pulmonary heart sound, diastolic gallop at the cardiac apex and pulsus alternans, (2) slight to moderate right ventricular failure—enlargement of the liver and slight to moderate dependent edema, (3) marked right ventricular failure—anasarca

Grade of Fever —(0) no fever, (1) slight fever—not over 1 degree (100.4 F, rectal), (2) moderate fever—1 to 2.5 degrees, (3) over 2.5 degrees

TABLE 1—*Entire Group (200 Patients, Including 50 Examined Post Mortem)*

Heart Failure		Fever				Sex		Age				Cause				
Grade	Number	None	1 Degree	2½ Degrees	Over 2½ Degrees	Male	Female	0 to 20	20 to 40	40 to 60	60 to 80	Rheumatic	Hypert	Coronary	Hyp & Cor	Miscellaneous
1 Slight	16 8%	0	4	4	8	12	4	2	3	4	7	4	6	2	2	2
2 Moderate	71 35.5%	3	14	19	35	38	33	13	19	26	13	37	6	11	3	14
3 Marked	113 56.5%	1	22	42	48	77	36	7	14	48	44	39	23	7	17	27
Total	200	4	40	65	91	127	73	22	36	78	64	80	35	20	22	43
Percentage		2	20	32.5	45.5	63.5	36.5	11	18	39	32	40	33.5			21.5

Entire Series —Of the 200 patients studied (table 1), 127 were males and 73 were females, 16 had left ventricular failure alone, 71 slight to moderate right ventricular failure, and 113, or over half, marked right ventricular failure Twenty-two patients were below 20 years of age,

4 Oral temperatures are notoriously unreliable as an indication of internal body temperature in the presence of dyspnea, which so often necessitates mouth breathing with resultant cooling and drying of the mucous membranes of the mouth

5 Left ventricular failure alone, usually based on the symptom of dyspnea in cases with cardiac enlargement secondary to systemic hypertension, aortic valvular disease or large myocardial infarcts, is graded as 1 with reference to extent of stasis, moderate or marked pulmonary vascular engorgement occurring only transiently in attacks of paroxysmal dyspnea in a few of the cases, right ventricular failure, as a rule secondary either to failure of the left ventricle or to disease of the mitral valve, is graded as 2 and 3, respectively, because of the obvious and chronic generalized stasis in the systemic circulation

36 were from 20 to 40, 78 were from 40 to 60, and 64 were from 60 to 80. As to the cause, rheumatic heart disease heads the list, with a total of 80 patients (40 per cent), 77 other patients had hypertensive, hypertensive and coronary or coronary heart disease, while the remaining 43 had one of the various other types of disease of the heart. Only 4 patients of the whole series of 200 were entirely free from fever during their stay in the hospital, and yet 3 of these 4 patients had moderate failure and 1 had marked failure. It is interesting to note that 48, or less than 50 per cent, of the 113 patients with marked failure had fever of over 2.5 degrees, whereas 8 of the 16, or exactly 50 per cent, of the group with slight failure had fever of over 2.5 degrees.

TABLE 2—Cases in Which Autopsy Was Performed

Heart Failure		Fever				Complications								
Grade	Number	None	1 Degree	2½ Degrees	Over 2½ Degrees	Pulmonary Infarction	Broncho pneumonia	Other Respiratory Infections	Active Rheumatic Infection	Acute Coronary Thrombosis	Other Complications	Questionable	Number With out Compli cations	
1 Slight	5 10%	0	0	1	4	3	2	0	0	1		0	0	
2 Moderate	18 36%	0	1	1	16	6	8	1	3	4	Cerebral hemorrhage, subacute bacterial endocarditis, parotitis, cerebral embolism	0	0	
3 Marked	27 54%	0	1	12	14	15	10	2	5	3	Pyelonephritis, cerebral thrombosis, infarction of spleen, infarction of pancreas, subacute bacterial endocarditis and rheumatic arthritis, septicemia	0	0	
Total	50	0	2	14	34	24	20	3	8	8	11	0	0	
Percentage			4	28	68	48	40	6	16	16	22			

Fatal Termination, Autopsy Performed—Table 2 presents data for the 50 cases in which autopsy was performed. There were 5 patients with grade 1 heart failure in this group, 1 of whom had 2.5 degrees of fever and others over 2.5 degrees. All 5 patients had complications. Three had pulmonary infarction, 2 had bronchopneumonia, and 1 had acute coronary thrombosis.

In the same group of 50 patients there were 18 with grade 2 heart failure. One had 1 degree of fever, 1 up to 2.5 degrees and the remaining 16 over 2.5 degrees. All 18 had complications, several more than one. Six had pulmonary infarction, 8 bronchopneumonia, 1 pneumonitis, 3 active rheumatic infection, 4 acute coronary thrombosis and 4 other complications as listed in table 2.

Twenty-seven of the 50 patients had grade 3, or marked, heart failure. One had up to 1 degree F of fever, 12, up to 2.5 degrees, and 14, over 2.5 degrees. All 27 had complications. Fifteen had pulmonary infarction, 10 bronchopneumonia, 2 pneumonitis, 5 acute rheumatic infection, 3 acute coronary thrombosis and 7 one of the other complications noted in the table.

In this group of 50 patients there were none without fever and, likewise, none without at least one complication that could be responsible for fever. In several instances there was more than one complication that might have caused the fever.

TABLE 3—Fatal Cases in Which No Autopsy Was Performed

Grade	Number	Fever				Complications						Questionable Number With out Complications
		None	1 Degree	2½ Degrees	Over 3½ Degrees	Pulmonary Infarction	Broncho pneumonia	Other Respiratory Infections	Active Rheumatic Infection	Acute Coronary Thrombosis	Other Complications	
1 Slight	1 3.2%	0	0	0	1	1	0	0	0	0		0
2 Moderate	14 45%	0	1	2	11	6	3	0	5	0	Cerebral embolism	1
3 Marked	16 51.6%	0	2	4	10	2	2	1	4	2	Embolism in leg, acute polyserositis, cerebral hemorrhage	3
Total	31	0	3	6	22	9	5	1	9	2	4	4
Percentage			9.6	19.3	70.9	29	16.1	3.2	29	6.4	12.9	12.9

Thus, of these 50 patients, a total of 48 per cent had pulmonary infarction, 40 per cent bronchopneumonia, 16 per cent acute rheumatic infection and 16 per cent acute coronary thrombosis. There was no patient with congestive heart failure alone and no patient without fever.

Fatal Termination, No Autopsy—Table 3 presents data for the 31 patients in whose cases death occurred and autopsy was not performed. In this group 1 patient had grade 1 heart failure, 14 grade 2 failure and 16 grade 3, or marked failure. Twenty-seven of the 31 patients had a known complication that could account for fever, and the remaining 4 patients had questionable complications—that is, complications were suspected but not definitely diagnosed. In this entire group of 31 patients, 29 per cent had pulmonary infarction, 16.1 per cent bronchopneumonia, 29 per cent active rheumatic infection and 6.4 per cent acute coronary thrombosis.

Surviving Group—Table 4 presents data for the surviving group—that is, the patients that were discharged alive from the hospital. In this group of 119 patients, 10 had grade 1 heart failure, 38 grade 2 failure and 71 grade 3, or marked, failure. The incidence of fever in relation to heart failure was approximately the same as it was in the previous groups, but complications were diagnosed less frequently. Fourteen per cent of the patients had pulmonary infarction, 7.5 per cent bronchopneumonia and 17.6 per cent active rheumatic infection. The diagnosis of acute coronary thrombosis was not made. In 28 patients a complication was suspected, but in 26 others it was neither diagnosed nor suspected. Of the latter 26 patients, 4 had no fever and 16 had fever.

TABLE 4—*Surviving Group*

Heart Failure		Fever			Complications							Questionable Number Without Evident or Question- able Complications
Grade	Number	None	1 Degree	2½ Degrees	Over 2½ Degrees	Pulmonary Infarction	Broncho- pneumonia	Other Respira- tory Infections	Active Rheu- matic Infection	Acute Coro- nary Throm- bosis	Other Complications	
1 Slight	10 8.4%	0	4	3	3	3	2	0	2	0		1 2
2 Moderate	38 31.9%	3	12	15	8	4	1	6	12	0	2, infection of urinary tract, 2, streptococcal sore throat	6 6
3 Marked	71 59.6%	1	19	27	24	10	6	4	7	0	Cerebral infarction, renal infarction, renal infection, 2 cystitis	21 18
Total	119	4	35	45	35	17	9	10	21	0	9	28 26
Percentage		3.3	29.4	37.8	29.4	14.2	7.5	8.4	17.6	0	7.5	23.5 21.8

of only 1 degree (F). Perhaps if a more diligent effort had been made to determine the cause of obscure fever in these cases, a greater number of complications might have been found.

COMMENT

Cohn and Steele³ observed that in their series of cases fever and heart failure disappeared simultaneously. We have not found this to be true in our series; instead, it is apparent that in many instances the elevation in temperature was related to the complication rather than to the heart failure, occurring as it did with or after the development of a complication. For example, 1 patient, a 24-year-old man, entered the hospital in November 1935; the diagnosis included rheumatic heart disease, mitral stenosis and regurgitation, auricular fibrillation and marked heart failure. He remained in the hospital three weeks, during

which time he was fever free and there was no evidence of active infection. He was readmitted on Jan 17, 1936, with marked heart failure, as before, and remained in the hospital until March, during this time leukocytosis developed, and he had other evidence of active rheumatic infection. His temperature became elevated to 101.4 F (rectal).

In the cases of some of our patients who were admitted with congestive heart failure and a complication such as bronchopneumonia or pulmonary infarction, the fever, heart failure and complication all subsided simultaneously. In a number of these instances it is certain that the complication was the chief factor responsible for the heart failure.

It has been asked whether complications may not occur without fever. No doubt this is occasionally true, as shown by one of our patients, who had two hospital visits. A girl 13 years of age was admitted to the hospital Oct 25, 1935. The diagnosis was rheumatic heart disease with mitral stenosis and regurgitation, active rheumatic infection and marked congestive heart failure. She had leukocytosis throughout her nine day stay in the hospital, the highest count being 20,000, but at no time did her rectal temperature go above 99.4 F. The patient was readmitted Aug 24, 1936, with the same diagnosis, and died Nov 8, 1936. During this period her rectal temperature remained below 99.4 F for the most part, on one occasion it was elevated to 101 F.

Our experience in this case, and in other cases of infectious disease not in the present series demonstrates the well recognized facts (1) that sometimes infections occur without fever, (2) that for certain persons a high "normal" temperature really means fever and (3) that, conversely, half a degree or so of "fever" may be normal for certain persons when excited or very restless. All of these considerations must be taken into account in each case of congestive heart failure as much as in a case of any other disease.

No doubt small infarctions of the heart or lung may occur without causing fever, as is true of active rheumatic fever, or the fever in these conditions may be of short duration or unusual periodicity so that it is missed, unless the temperature is taken often.

Only 1 case of congestive heart failure precipitated by paroxysmal tachycardia was included in our study. A small boy, 4 years of age, had two admissions to the hospital. At the time of the first hospitalization, from May 13 to June 22, 1933, the diagnosis was paroxysmal tachycardia and acute tonsillitis. The temperature was elevated during the first part of the stay in the hospital, as a result of the tonsillitis, the highest reading being 102 F (rectal). Mild congestive failure developed after prolonged paroxysmal tachycardia. The second admission was on July 20, 1933, and the patient died seven days later, after a cerebral infarction,

which occurred early on the day of death. Postmortem observations were as follows: cardiac hypertrophy, mural thrombus, left ventricular wall; cerebral embolism and infarction, congenital bicuspid aortic valve; endocarditis, diffuse thickening of the endocardium, bilateral hydrothorax, hydropericardium, and pulmonary congestion. The rectal temperature at no time was higher than 99.4 F until the seventh day, before death, when, owing to the cerebral infarction, it was 101.8 F.

Emerson,⁶ in discussing pulmonary infarction, noted that patients often show temperatures of 99 to 100 F daily for a week or two previous to pulmonary infarction—evidence probably of thrombophlebitis. Assuming that this is true, it is possible that a certain number of patients may have concealed thrombophlebitis which would account for fever, without actual development of pulmonary infarction.

The basal metabolic rate in some cases of congestive heart failure is considerably above the normal level. The cause of this elevation is not entirely understood, but it is thought to be due to the increased work of the body as a result of such symptoms as dyspnea and cough, also, the myocardium itself consumes more than its normal amount of oxygen, owing to its increased bulk and inefficiency. In our series, however, the basal metabolic rate was elevated to plus 20 per cent or more in only 3 of the 12 cases of congestive failure in which the rate was determined. In none of the 3 was there thyrotoxicosis, so far as could be determined. No basal metabolic rate was as high as plus 40 per cent, despite the presence of fever in all 12 patients and of complications in most of them. A complication inducing fever is probably more likely than is congestive heart failure itself to raise the basal metabolic rate.

SUMMARY AND CONCLUSIONS

Two hundred cases of congestive heart failure have been reviewed to determine the incidence and cause of fever in this condition.

In 81 of the cases the patients died, and in 50 cases autopsy was performed. At least one complication was found in each of these 50 cases to which might be attributed the fever that had been present. In all of the remaining 31 cases in which autopsy was not performed fever was present, and in 27 of these a complication which could account for fever was found, in the other 4 cases such a complication was suspected but was not proved.

In 119 cases the patients survived, fever was present in all but 4, and in these 4 cases no complications were found. A complication was diagnosed or suspected in 93 of the 119 cases. In 22 cases in which fever

⁶ Emerson, C. P., in Cecil, R. L. *A Textbook of Medicine*, ed. 4, Philadelphia, W. B. Saunders Company, 1937, p. 866.

was present a complication was neither diagnosed nor suspected, in 16 of these the fever was of only 1 degree (F) or less

Thus, although congestive heart failure alone may possibly explain up to 1 degree of fever, there was almost invariably some underlying complication to account in general for fever in the cases of congestive heart failure which we have studied. In order of frequency the four most common complications were pulmonary infarction, pulmonary infection (especially bronchopneumonia), active rheumatic infection and acute coronary thrombosis.

Fever of any grade in a case of congestive heart failure should be considered as probable evidence of some complicating condition, which not only frequently explains intractability to treatment but also may be the cause of death, which rarely occurs with heart failure alone.

BASAL SECRETION OF DIGESTIVE ENZYMES IN OLD AGE

JACOB MEYER, M D

E SPIER, M D

AND

F. NEUWELT M D

CHICAGO

In a previous communication¹ we reported that salivary ptyalin is diminished in the aged. The present study was undertaken to determine the activity under fasting conditions of the enzymes in saliva, in gastric juice and in duodenal juice by several of the newer enzyme methods as well as to compare any further differences in enzyme activity between these various secretions in young and in old persons.

MATERIAL AND METHOD

A total of 61 subjects were tested, 29 of them being between 60 and 96 years of age and the remainder 32, varying in age from 12 to 60 years. Normal subjects were tested, but most of the members of the older age group showed one or another of the infirmities of old age. Most of the old subjects were residents of a home for the aged. The younger group consisted of suitable clinical patients, interns and graduate students.

The ptyalin content of the saliva was tested by two methods: (a) the Wohlgemuth method as described by Hawk and Bergheim,² one unit of ptyalin is expressed as the amount required to digest 5 cc. of a 2 per cent starch solution to the achromic point, and (b) the method of Ross and Shaw,³ one unit of amylase is the amount of enzyme which will liberate 5 mg. of maltose under the conditions described in this communication.

For determination of the values for pepsin and trypsin we used the methods of Anson and Mirsky.⁴ Pepsin: The activity of the enzyme is determined by comparing its ability to form tyrosine in five minutes with a standard solution containing 0.15 mg. of tyrosine. Trypsin: The tyrosine formed by the enzyme in five minutes is compared with a standard solution containing 0.25 mg. of tyrosine.

From the Departments of Medicine, of Gastrointestinal Research and of Chemistry, Michael Reese Hospital.

1 Meyer, J.; Golden, J. S., Steiner, N., and Necheles, H. The Ptyalin Content of Human Saliva in Old Age, *Am. J. Physiol.* **119**: 600, 1937.

2 Hawk, P. R., and Bergheim, O. *Practical Physiological Chemistry*, ed 10, Philadelphia, P. Blakiston's Son & Co., 1931, p. 263.

3 Ross, J. R., and Shaw, M. M. Determination of Pancreatic Amylase, *J. Biol. Chem.* **104**: 131, 1934.

4 Anson, M. L., and Mirsky, A. E. Determination of Proteases, *J. Gen. Physiol.* **16**: 59, 1932; **17**: 151, 1933.

For determination of lipase the method of Cherry and Crandell ⁵ was used, after an incubation period of twenty-four hours the fatty acids are titrated with one-twentieth normal sodium hydroxide

All observations were made on fasting subjects, and the samples were put into an ice box immediately after collection. The saliva was collected after rinsing the mouth with water. The gastric and duodenal juices were aspirated by a rubber tube with a double lumen as used by Miller and Abbot ⁶. One tube, with a duodenal bucket attached to the tip, went down to the duodenum, and the other had openings approximately 15 cm above this point for aspiration of the gastric contents. These contents were continuously aspirated by siphonage into the flask which was placed about 30 inches (75 cm) below the level of the stomach, while the duodenal juice was aspirated by syringe. The first samples were discarded, and only the bile-stained alkaline juice was tested. One hour was generally required to intubate the duodenum. In about 15 per cent of all cases we did not obtain the duodenal juice, because the tube was doubled in the stomach or would not pass into the duodenum.

RESULTS AND COMMENT

The concentration of ptyalin in the saliva of old persons as determined by the Wohlgemuth method is less than one third of the amount present in the saliva of young persons, but by the method of Ross and Shaw the concentration of ptyalin for the older group is about two thirds of that for the control group (chart 1). Olson, Fricke and Kaja ⁷ assumed the presence of two enzymes in saliva, which are differentiated by their effect on carbohydrates, the amylolytic action and the maltose-forming effect. The Wohlgemuth iodine reaction shows only the digestion of starch to achroodextrin (amylolytic action), whereas the other method indicates the amount of maltose formed. This fact may explain the difference in our results as obtained by these two methods. The concentration of sodium chloride in the enzyme systems tested by the two methods may influence the results, but we found that different concentrations of sodium chloride affected the results very little. It is evident that in aged persons salivary amylase is decreased. This confirms our previous studies.

The concentration of pancreatic amylase (chart 2) is subnormal in old age. It is interesting to note that in the age group between 81 and 100 we found values which reached the average level for the younger group. The higher value for pancreatic amylase may be a substitute for the lower value for salivary ptyalin in old age. Our results suggest that completion of the digestion of carbohydrates is not markedly disturbed in the aged.

⁵ Cherry, J. S., and Crandell, L. A. The Specificity of Pancreatic Lipase, *Am J Physiol* **100** 266, 1932

⁶ Miller, J. G., and Abbot, W. O. Intestinal Intubation. A Practical Technique, *Am J M Sc* **187** 595, 1937

⁷ Olson, Fricke and Kaja, cited by Oppenheimer, C. Die Enzyme und ihre Wirkungen, The Hague, W. Junk, 1933

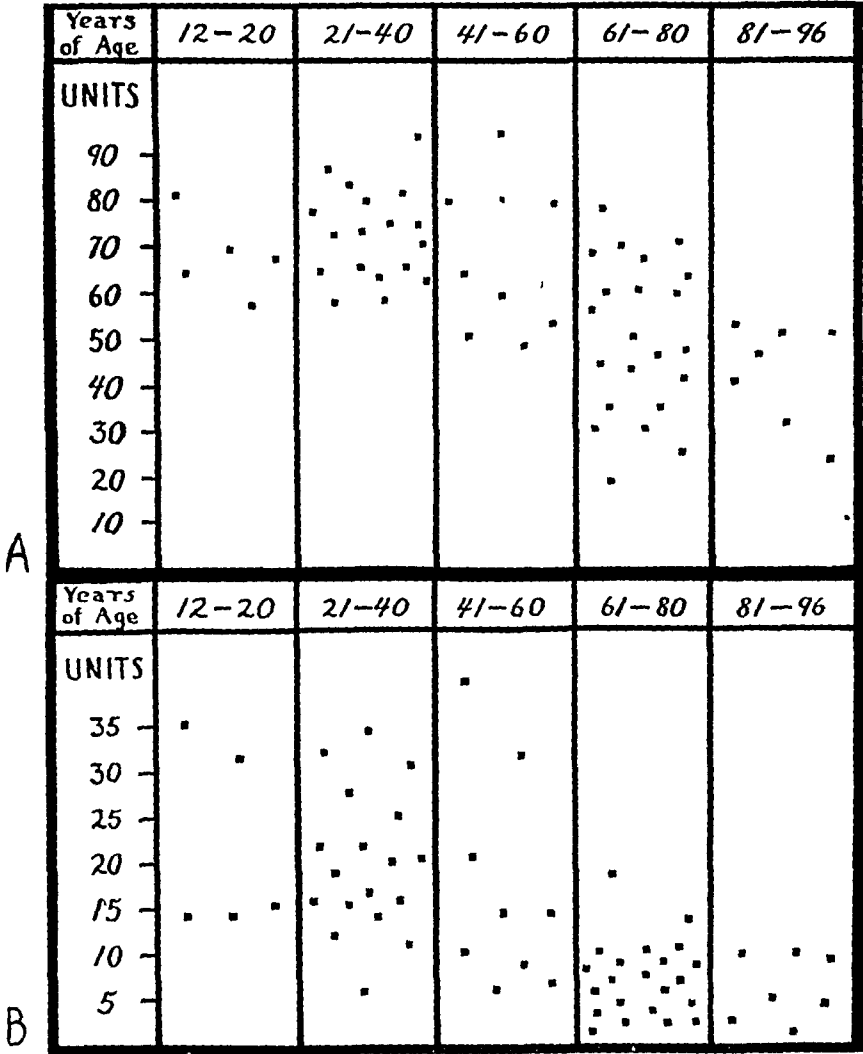


Chart 1—*A*, salivary ptyalin estimated by the Shaw and Ross method The enzyme activity falls little in the older age groups, although a downward trend is evident The reaction is carried to completion, i e, to the formation of maltose *B*, salivary ptyalin estimated by the Wohlgemuth method The concentration of ptyalin falls markedly about the sixtieth year of life This reaction involves only the first step in the breakdown of starch to achroodextrin (amylolytic action)

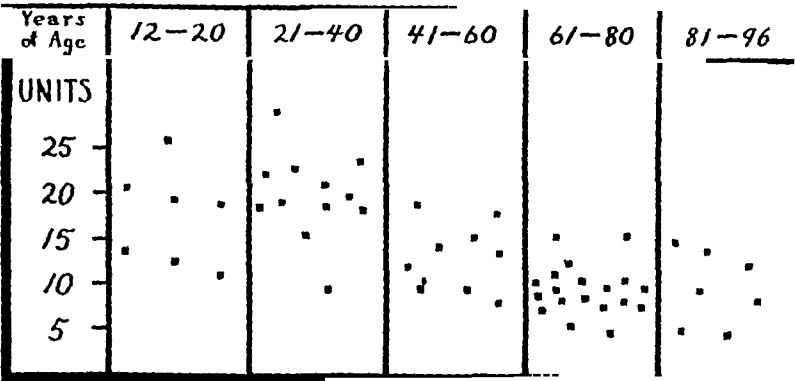


Chart 2—Pancreatic amylase This graph is rather similar to chart 1 *A*, except that the units are much less It is obvious from the chart that the aged need suffer no embarrassment of carbohydrate digestion

We determined the values for free and total acid as well as for pepsin in all cases. In about 35 per cent of the younger subjects and in about 65 per cent of the aged subjects there was no free acid in the "fasting" gastric contents. Occasionally we found a relatively high value for pepsin, but we could not find any correlation between the concentrations of acid and pepsin in "fasting" gastric juice. We found a steady drop in acidity with advancing age. Similar observations have been published by Bloomfield,⁸ Sagal, Marks and Kantor⁹ and others. Mullins and Flood¹⁰ found a high correlation between acid and pepsin secretion in response to a test meal, though exceptions were not infrequent. In general, a high value for acid was likely to be accompanied by a high

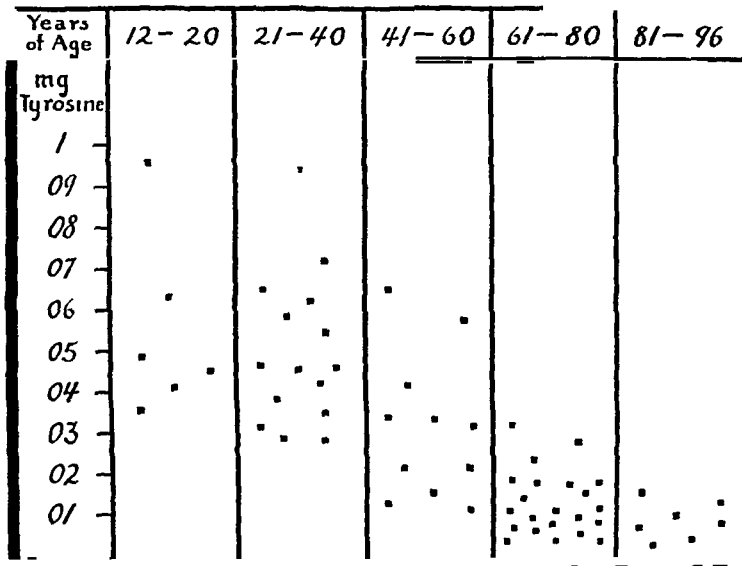


Chart 3—Pepsin. The concentration falls sharply during the seventh decade of life and after that maintains a rather constant low value.

value for pepsin, and vice versa. According to our observations there was no evidence of such relations in "fasting" gastric juice.

The concentration of pepsin (chart 3) is low in old persons. In the younger group it shows great variability, but it has rather constant low values for old persons. Osterberg, Vanzant, Alvarez and Rivers¹¹

8 Bloomfield, A. L. The Mechanism of Decrease of Gastric Secretion with Advancing Years, *Am J M Sc* **190** 325, 1935.
9 Sagal, Z., Marks, J. A., and Kantor, J. L. The Clinical Significance of Gastric Acidity, *Ann Int Med* **7** 76, 1933.
10 Mullins, C. R., and Flood, C. A. A Study of Gastric Pepsin in Various Diseases, *J Clin Investigation* **14** 793, 1935.
11 Osterberg, A. E., Vanzant, F. R., Alvarez, W. C., and Rivers, A. B. Studies of Pepsin in Human Gastric Juice, *Am J Digest Dis & Nutrition* **3** 35, 1936.

made analyses of gastric juice of 6,200 patients and our observations parallel theirs closely in that values for pepsin fluctuated widely in the cases of young persons. These authors found the secretion of pepsin to decrease with age much as does the secretion of acid.

The concentration of trypsin (chart 4) in our cases was similar to that of pepsin except that the values for the younger group did not show such extreme variations as in the case of pepsin and that a drop in the values after the fortieth year of life was observed.

Both proteolytic enzymes were present in the aged, in a concentration one fourth that in the control group. It is usually stated that the pancreas secretes when the gastric hydrochloric acid acts on the duodenal mucosa. We found no evidence of pancreatic hypofunction in cases of

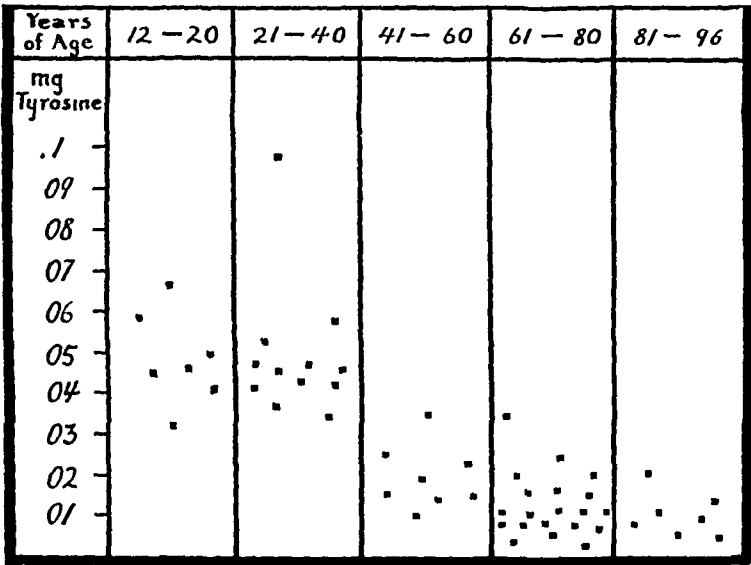


Chart 4—Trypsin. The tryptic activity falls sharply after the fortieth year of life. The proteolytic powers of pancreatic juice bear no relation to gastric acidity.

achlorhydria or subacidity. This point may be illustrated by means of two typical protocols, one from the control and one from the old age group.

Relation of Gastric Acidity to Pancreatic Activity		
	E L, aged 42	N S, aged 76
Free acid	0	0
Total acid	0	0
Pancreatic amylase	12 units	16 units
Pancreatic trypsin	0.034 mg	0.006 mg
Pancreatic lipase	3.35 cc	2.42 cc.

In the first case the concentrations of the three enzymes were within normal limits, in the second case amylase and lipase showed normal values, trypsin being diminished but falling in line with our results for

old persons McClure¹² stated that the normochylic reaction is characterized by an ample quantity of pancreatic juice of low enzyme concentration, whereas the achylic is characterized by a smaller quantity of juice of higher enzyme concentration Calculating the average total quantity of trypsin, McClure concluded with regard to the digestive function that the secretion of duodenal juice both in the achylic and in the normochylic subject finally attains the same efficiency

It should be emphasized that in our own series enzyme activity, determined on fasting persons, showed no correlation between gastric acidity and trypsin concentration The main determinant of the activity of trypsin is apparently age McClure's subjects were fed a bread meal to stimulate duodenal secretion, and the trypsin concentration was

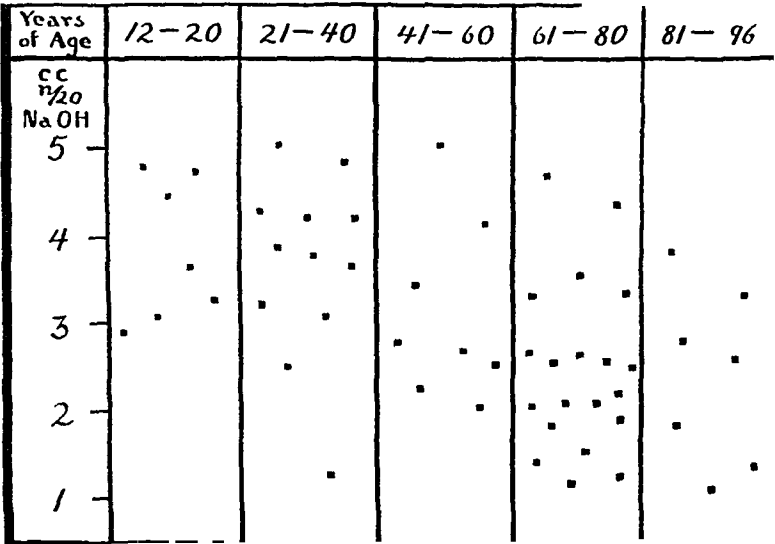


Chart 5—Pancreatic lipase The lipolytic activity of pancreatic juice is variable and is dependent neither on gastric acidity nor on the age of the subject

apparently conditioned by the gastric acidity In view of our own findings in fasting subjects, his conclusions may be subject to some doubt Furthermore, the values for trypsin obtained by us showed the maximum enzyme activity of each individual sample, since the analytic method employed avails itself of the optimum p_H for the reaction

It is known that the concentration of lipase in pancreatic juice is subject to great variation This also is in keeping with our results We found that the activity of lipase (chart 5) is slightly diminished in the aged, but it is unlikely that the diminished activity interferes with the hydrolysis of fat in the food

12 McClure, C W Functional Activities of the Pancreas and Liver A Study of Objective Methods for the Estimation of Function Levels in Health and Disease, New York, Medical Authors' Pub Co, 1937

The average values for all enzymes for our female subjects, both old and young, were slightly lower than those for males

There is no literature concerning the activity of enzymes in old age. In spite of the low concentration of the proteolytic enzymes indicated by our results, nothing has been written about special difficulties of old persons in the digestion of proteins. The problem of mastication often necessitates the use of a soft diet which is relatively high in carbohydrate and low in proteins. It is known that institutions for the aged serve a diet high in carbohydrate and low in proteins. As we have noted, the digestion of carbohydrates is not markedly disturbed in old persons. It is likely that, even though the concentration of proteolytic enzymes is low, it is adequate to meet the requirements of the small protein intake. We are aware from clinical experience that there are old persons whose protein intake is fairly large and who have no difficulty in digestion. It is possible that the character of the food may be a factor in the secretory response.

It would be of interest to determine the secretory responses to various types of food and to various stimulants of gastric and pancreatic secretion, such as histamine, alcohol, olive oil and secretin. This we hope to report in the future.

The question might be raised whether our results are due to physiologic changes or to gastritis, which may accompany old age. None of the subjects had a history of gastritis or symptoms indicating clinical gastritis, we therefore regard them as normal old persons. It would be extremely interesting to correlate our results with gastroscopic observations. This we hope to do at a future date.

SUMMARY

- 1 The fasting concentrations of salivary ptyalin, of gastric pepsin and of pancreatic amylase, trypsin and lipase were determined in a group of 32 subjects between 12 and 60 years of age and in a group of 29 subjects between 60 and 96 years of age.

- 2 Old persons show a deficiency in the concentration of salivary amylase and slightly subnormal values in the concentration of pancreatic amylase.

- 3 Both proteolytic enzymes (pepsin and trypsin) are diminished in the aged and therefore cannot compensate for each other.

- 4 The concentration of lipase was found to be relatively unchanged in old age.

- 5 Subacidity and anacidity did not influence either the activity of the proteolytic enzymes or the secretory action of the pancreas.

- 6 These studies may be important in the dietary management of old persons.

CLINICAL STUDIES IN CIRCULATORY ADJUSTMENTS

VI PHYSIOLOGIC RELATION BETWEEN POSTURE AND CARDIAC OUTPUT

A ALLEN GOLDBLOOM, M D

Associate Physician, Beth Israel and Metropolitan Hospitals, Associate
Cardiologist, Beth Israel Hospital, Instructor in Medicine,
New York Medical College

MILTON L KRAMER, M D

Adjunct Physician and Assistant Cardiologist, Beth Israel Hospital, Instructor
in Medicine, Cornell University Medical College

AND

ABRAHAM LIEBERSON, M D

Adjunct Physician and Assistant Cardiologist, Beth Israel Hospital, Clinical
Assistant Visiting Physician, Second (Cornell)
Division, Bellevue Hospital

WITH THE TECHNICAL ASSISTANCE OF PAUL K ROHT
NEW YORK

When man assumed an upright posture he added appreciably to the adaptive needs of his circulation. New vasomotor regulations became necessary to counteract the effects of gravity. Inadequacies of these regulatory processes, whether congenital or acquired, are of importance to the clinician, who is confronted not infrequently with patients presenting untoward symptoms after a change in posture. Although the effects of gravity are greater on the venous than on the arterial side, there are so many factors which compensate for this primary effect on the venous return that the net change in the circulation produced by change in position can best be studied in terms of cardiac output. The reports in the literature on the effect of change of posture on cardiac output are so conflicting that a corroborative study of this subject by the highly satisfactory Grollman method was undertaken.

From the Medical Service of Dr. I. W. Held and the Laboratory Department of the Beth Israel Hospital.

This study was made possible through the establishment of a fund for this purpose by Henry W. Dazian.

MATERIAL AND METHOD

In the present study (the sixth in a series "Clinical Studies in Circulatory Adjustments"¹), cardiac output after alteration of posture was determined for 6 normal subjects, 5 hypertensive subjects, 3 patients with neurocirculatory asthenia, 5 patients with organic heart disease (chronic cardiac valvular disease and disease of the coronary arteries) and 4 patients with anemia

A modification of the Grollman acetylene method was utilized according to the specifications published in another paper by one of us^{1c}. The Grollman method is preferable to others in that it is the simplest and the least objectionable to the patient

The normal subjects were interns and laboratory attendants, the patients were from the inpatient and outpatient departments of the hospital. The tests were performed at least six to eight hours after the subject had eaten a meal, and the determinations were made with the subject in four positions: (1) recumbent, (2) with feet elevated, (3) sitting and (4) standing. The subject was kept in the recumbent position for an hour to allow an approach to a basal state, tight clothes were loosened and shoes removed, a small pillow was used to add to the comfort of this position. At the end of the hour the pulse, blood pressure and oxygen consumption were determined, followed by determination of the value for arteriovenous oxygen difference. After fifteen minutes the acetylene rebreathing was repeated. The patient's lower extremities were then elevated by raising the lower third of the bed to an angle of 45 degrees with the body. This position was maintained for thirty minutes, after which time the determinations were made, the rebreathing was repeated in fifteen minutes. This check was carried out with the subject in each position. Subsequently the subject was allowed to sit in a comfortable chair with the back supported for one-half hour, when the determinations again were made. After this the standing position was assumed for a thirty minute period. Whenever possible the tests were performed with the subject in the four positions. In some instances, however, it was necessary to shorten the procedure, omitting the sitting posture, since it represents an intermediate stage between the recumbent and the upright position. The study of the 23 subjects included a total of seventy-eight positions.

SUMMARY OF FINDINGS

Analysis of the 6 normal subjects (see table) showed that change of position had practically no effect on blood pressure. With the subject standing there was a slight increase in pulse rate. The cardiac output remained practically unchanged with all positions, but the cardiac stroke was diminished when the subject stood or assumed the position of recumbency with the feet elevated.

1 (a) Goldbloom, A. A., Libin, I., and Roht, P. K. Clinical Studies in Circulatory Adjustments. I. Clinical Evaluation of Studies of Circulating Blood Volume, *Arch Int Med* **55** 484 (March) 1935. (b) Goldbloom, A. A., and Bauer, H. E. Clinical Studies in Circulatory Adjustments. II. Venous Pressure, a Simple Bedside Method, *Collect Papers New York Homeop M Coll* **1** 45, 1935. (c) Goldbloom, A. A., and Roht, P. K. Clinical Studies in Circulatory Adjustments. III. Clinical Evaluation of Cardiac Output Studies, *Internat Clin* **3** 206, 1936. (d) Rothschild, M. A., and Goldbloom, A. A. Clinical Studies in Circulatory Adjustments. IV. Obliterating Pulmonary Arteritis with Secondary Pulmonary Changes and Right Ventricular Hypertrophy, Report of a Case with Autopsy, *Arch Int Med* **61** 600 (April) 1938. (e) Goldbloom, A. A., and Lieberman, A. Clinical Studies in Circulatory Adjustments. V. Clinical Evaluation of Cardiodynamic Studies, *Am J M Sc* **197** 182, 1939.

The patients with hypertension had a slightly increased pulse rate in the standing and sitting positions. There was no significant change in cardiac output with the various positions. The cardiac stroke was slightly increased with elevation of the feet but was essentially unchanged with all the other postures.

The group of patients with neurocirculatory asthenia had an increased pulse rate in the sitting and standing positions. Cardiac output and cardiac stroke, however, were not significantly altered.

The patients with organic heart disease showed a slight increase in cardiac output in the upright positions, especially in the sitting posture. These findings

Average Values for Various Groups

Condition	Number of Subjects	Body Surface, Square Meters	Blood Pressure	Pulse Rate	Oxygen Consumption, Cc/Min	Arterovenous Oxygen Difference, Cc/Liter	Cardiac Output, Liters/Min	Cardiac Output per Beat, Cc	Cardiac Index, Liters
Normal	6	1.75							
Recumbent			110/70	73	228	58	3.99	53	2.28
Feet elevated			118/80	80	236	63	3.81	46	2.18
Standing			116/80	84	260	65	3.98	47	2.27
Sitting			105/69	76	242	60	4.01	52	2.29
Hypertension (compensated)	5	1.71							
Recumbent			180/106	82	244	59	4.14	50	2.42
Feet elevated			176/109	82	265	61	4.35	52	2.54
Standing			170/105	86	264	63	4.19	48	2.45
Sitting			176/107	85	277	64	4.34	50	2.54
Neurocirculatory asthenia	3	1.67							
Recumbent			114/63	79	213	56	3.80	47	2.27
Feet elevated			109/63	80	224	58	3.86	47	2.31
Standing			102/65	92	241	61	3.92	42	2.34
Sitting			110/71	89	236	58	4.06	45	2.43
Cardiac disease	5	1.75							
Recumbent			159/90	83	237	62	3.82	46	2.18
Feet elevated			165/89	82	247	61	4.12	51	2.35
Standing			161/82	85	246	60	4.16	49	2.37
Sitting			160/86	88	268	58	4.66	53	2.66
Anemias	4	1.63							
Recumbent			118/78	74	224	62	3.64	51	2.23
Feet elevated			123/81	73	243	67	3.70	50	2.27
Standing			115/77	78	225	58	3.84	49	2.35
Sitting			110/65	88	220	53	4.15	47	2.54

are based on limited determinations for the upright and sitting positions because of the orthopnea of the patients. Care must be exercised, therefore, in interpreting the results.

Patients with various types of anemia also failed to show any significant change in the cardiac output on change of position.

GENERAL COMMENT

When one assumes the upright position, gravity exerts an effect on both the arterial and the venous tree, but especially on the latter, with its comparatively low head of pressure. As Hess² has pointed out, the

² Hess, W. R. Die Gesetze der Hydrostatik und Hydrodynamik, in Bethe, A., von Bergmann, G., Embden, G., and Ellinger, A. Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 7, pp. 888-933.

circulation is established to the advantage of the lower half of the body. The effect on the circulation is not marked if the venous side can maintain the return blood flow to the heart. Definite quantities of blood stagnate, however, in the lower extremities, as Atzler and Herbst³ showed in their plethysmographic studies and Parrisius⁴ with the capillary microscope. There is, furthermore, a diminution of the circulating blood volume with the body in the upright position, according to Eppinger,⁵ the blood stagnating in the blood depots of the hepatic-splanchnic region and the subcapillary cutaneous plexus.

The increased difficulty of venous return caused by reducing the diastolic filling of the heart would normally result in a lessened cardiac output, according to Starling's "law of the heart." There are, however, several important physiologic mechanisms which compensate in great part for this drop in stroke volume. Perhaps the most important of these is the carotid sinus apparatus, which suffers a diminution of tone when the stroke volume and blood pressure in the aorta fall. This produces reflexly an increase in pulse rate and a narrowing of the peripheral arterioles, with a resultant rise in diastolic pressure. It is likely that an insufficient blood supply to the vasomotor centers of the medulla acts in conjunction with the carotid sinus reflex to produce these effects. Less known reflexes from muscles, tendons, articular surfaces and walls of blood vessels in the lower extremities also may play a role. Thus, a change from a prone to an upright posture produces normally an average rise of 10 to 12 pulse beats and 8 to 10 mm of diastolic pressure, with a very slight drop (0 to 4 mm) in systolic blood pressure at the brachial artery (Ghrist⁶).

In general, these compensatory mechanisms suffice in the normal person to prevent distress. When gravitational shock does occur in man, some other disturbance of the circulatory mechanism is present (Macleod⁷). One encounters gravitational shock clinically in soldiers who have been standing rigidly at attention for too long a period, in vasolabile persons, in patients convalescing from severe illness and in

3 Atzler, E., and Herbst, R. Die Schwankungen des Fussvolumens und deren Beeinflussung, *Ztschr f d ges exper Med* **38** 137, 1923.

4 Parrisius, W. Der Blutstrom in den Hautkapillaren in verschiedenen Korperregionen bei wechselnder Korperlage, *Deutsches Arch f klin Med* **141** 243, 1922.

5 Eppinger, H. Zur Pathologie der Kreislaufcorrelationen, in Bethe, A., von Bergmann, G., Embden, G., and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1931, vol 16, p 2.

6 Ghrist, D. G. Circulation and Postural Change. *Adjustments in Health and Disease*, California & West Med **39** 161, 1933.

7 Macleod, J. J. R. *Physiology in Modern Medicine*, ed 8, edited by P. Bard, St. Louis, C. V. Mosby Company, 1938.

normal persons after vigorous exercise (Mateeff and Petroff⁸) It is usually explained as due to lack of the normal pumping action of the muscles and to ischemia of the vasomotor center because of reduced stroke volume

There is also a distinct clinical group of patients with "postural hypotension" who have syncopal attacks on alteration of position (Herz,⁹ Munzer,¹⁰ Martini and Pierach,¹¹ Bradbury and Eggleston¹²) They sustain a marked drop in blood pressure on assuming the upright position, but the pulse rate remains slow and unchanged Similar effects on blood pressure and attacks of syncope are frequently seen in cases of Addison's disease, but in this condition the pulse is usually rapid

The effects of postural change are more marked than normally in persons with varicose veins or with acrocyanosis Wollheim¹³ has described such persons as presenting marked stasis in the subpapillary plexus, with consequent diminution in the circulating blood volume when the body is in the upright position

From these clinical observations it would appear that gravity has an effect on the circulation which in the main is compensated for in the average person When one comes to the more scientific study of this subject, however, one encounters a confusing picture Historically the problem of alteration in cardiac output due to change in position was first approached through roentgen studies of the cardiac silhouette Moritz,¹⁴ Dietlen¹⁵ Vaquez,¹⁶ Groedel¹⁷ and others reported smaller

8 Mateeff, D, and Petroff, C Gravitationsschock beim Menschen nach Muskularbeit, Ztschr f d ges exper Med **85** 115, 1932

9 Herz, M Ueber Bradykardie, Hypotonie und hypotonische Bradykardie, Wien klin Wchnschr **23** 768, 1910

10 Munzer, E Zur Lehre von den vaskularen Hypotonien, Wien klin Wchnschr **23** 1341, 1910

11 Martini, P, and Pierach, A Die niedere Blutdruck und der Symptomenkomplex der Hypotonie, Klin Wchnschr **5** 1857, 1926

12 Bradbury, S, and Eggleston, C Postural Hypotension, Am Heart J **1** 73, 1925

13 Wollheim, E Die zirkulierende Blutmenge und ihre Bedeutung fur Kompensation und Dekompensation des Kreislaufs, Ztschr f klin Med **116** 269, 1931

14 Moritz, F Methodisches und Technisches zur Orthodiagraphie, Deutsches Arch f klin Med **81** 1, 1904

15 Dietlen, H Ueber die klinische Bedeutung der Veränderungen am Zirkulationsapparate insbesondere der wechselnden Herzgrosse bei verschiedener Körperstellung (Liegen und Stehen), Deutsches Arch f klin Med **97** 132, 1909

16 Vaquez, H Diseases of the Heart, translated by G F Landlaw, Philadelphia, W B Saunders Company, 1924

17 Groedel, F M Welche Momente bedingt die verschiedene Grosse respektive Form des vertikalen und des horizontalen Herzorthodiagrammes? Ann d stadt allg Krankenh zu Munchen **14** 328, 1910

measures of the heart shadow in orthodiagrams made when the subjects were in an upright position. This suggested a diminished volume of the heart, but it was not until methods of determination of cardiac output were perfected that conclusive data could be obtained to prove this. Lindhard,¹⁸ using the nitrous oxide method, reported diminution of the cardiac output with the subject in the upright position, but his findings are of questionable value, as his determinations for the various positions were made on different days. Collett and Liljestrand¹⁹ stated that they have confirmed Lindhard's findings, but they offered only a single experiment. Henderson²⁰ also reported a marked diminution in cardiac output with the subject in the upright position, but he used the ethyl iodide method, the results of which are questionable.

With the development by Grollman²¹ of the acetylene method, more accurate determination of the effect of posture on cardiac output became possible. Grollman, in an intensive study, failed to find any appreciable change, but Kylin,²² reviewing Grollman's figures found that they establish, at least statistically, a diminution of 0.21 liters (5 per cent) with the subject in the erect position. Kylin's own series indicates a diminution of 0.46 liters (11 per cent) with the subject in the erect position. Kroetz²³ found that the cardiac output with the subject in the prone position (average 4.42 liters) is greater than with the subject in the sitting posture (average, 3.5 liters) and is smallest of all with the subject in the erect position. Bielschowsky²⁴ and Fisher²⁵ have confirmed these findings.

Grollman ascribed the contradictory findings to the subjects' superficial breathing in the recumbent position, which, he contended, results in a poor mixture of the gases, with consequent lower arteriovenous oxygen differences and higher values for cardiac output. Fisher's

18 Lindhard, J. Effect of Posture on Output of Heart, *Skandinav Arch f Physiol* **30** 395, 1913.

19 Collett, M. E., and Liljestrand, G. Variations in the Resting Minute Volume of the Heart, *Skandinav Arch f Physiol* **45** 17, 1924.

20 Henderson, Y. Efficiency of the Heart and Its Measurement. Applications and Results on Man, *Lancet* **2**:1215 and 1317, 1925.

21 Grollman, A. The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

22 Kylin, G. The Relation Between Heart Volume and Stroke Volume in Recumbent and Rest Positions, *Skandinav Arch f Physiol (supp.)* **69** 237, 1934.

23 Kroetz, C. Messung des Kreislaufminutenvolumens mit Acetylen als Fremgas, *Klin Wchnschr* **9** 966, 1930.

24 Bielschowsky, P. Ueber den Einfluss des Lagewechsels insbesondere der Beinhochlagerung auf das Minutenvolumen des Herzens bei gesunden und kranken Menschen, *Klin Wchnschr* **11** 1252, 1932.

25 Fisher, I. L. Das Schlag- und Minutenvolumen des menschlichen Herzens bei verschiedenen Körperstellungen, *Arbeitsphysiol* **6** 111, 1932.

results are questioned because of the variation in his values for oxygen utilization by the same patient in the same position on various days Schellong,²⁶ like Grollman, has been unable to find significant changes in cardiac output and has ascribed the diminution found by other workers to changes due to the long period of standing required by the methods used. He found that the cardiac output drops on quiet standing, largely because of a drop in the rate of oxygen consumption.

Bock,²⁷ using a tilting table to eliminate the effect of muscular activity, obtained a 24 per cent diminution of cardiac output with the subject in the upright position. This was more marked in patients convalescing from various diseases (30 per cent) and still more noticeable in a group of vasolabile patients (34.6 per cent). Determinations on 3 trained patients revealed less diminution in cardiac output (i. e., from 3 per cent to 10 per cent), whereas in 1 subject, an athlete, there was actually an increase from 7.9 to 16.2 per cent. These findings are important in that they call attention to two significant factors in adaptation of the circulation to a change in position. These are muscular activity and the condition of the patient as influenced favorably by training or adversely by disease. Diverse results in the literature may conceivably be due to varying degrees of muscular activity and differing states of physical fitness in "healthy" subjects or of inaccuracies introduced by the stringent requirements of the experimental procedure, which interfere with the free play of the patient's compensatory mechanisms.

CONCLUSION

It has been our purpose in this study to determine whether alteration of posture produces a definite change in cardiac output. A number of authors have reported a marked effect on cardiac output due to change in position, others have reported little effect. Using the Grollman acetylene method with 23 subjects (normal persons, hypertensive persons, patients with cardiac disease and patients with various anemias and blood dyscrasias), we found little, if any, change in the cardiac output on change of position. Our results are in close agreement with those obtained by Grollman.

The conclusion is reached that the practically unaltered cardiac output demonstrated by the subjects studied in four different postures is indicative of the ability of the human organism under natural circumstances to compensate for the changes induced by the force of gravity.

26 Schellong, F. Klinische Untersuchungen über Kreislaufregulation in aufrechter Körperstellung, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1933, p. 176. Schellong, F., and Heinemeier, M. Ueber die Kreislaufregulation in aufrechter Körperstellung und ihre Störungen, Ztschr. f. d. ges. exper. Med. 89: 49 and 61, 1933.

27 Bock, H. E. Das Minutenvolumen des Herzens im Liegen und Stehen, Ztschr. f. d. ges. exper. Med. 92: 782, 1934.

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1939

FRANCIS M RACKEMANN, M D

Associate in Medicine, Harvard Medical School, Physician and Chief of
Allergy Clinic, Massachusetts General Hospital

BOSTON

Last year I¹ wrote "Each year the papers written on allergy cover a wider territory" Now the situation is becoming even more complicated because it appears that certain symptoms, like asthma, may come from causes which are not allergy at all, though the clinical pictures seem to be quite the same as in the typical cases of allergy "All is not allergy that wheezes," and, by the same token, sneezes and itches of various kinds which seem like allergy may not be due to allergy in the ordinary clinical sense In a recent discussion of the relation between anaphylaxis and allergy, Dragstedt² points out that whereas histamine, heparin and possibly other agents are liberated easily from sensitive cells as a result of the specific antigen-antibody reaction, the same substances may be released from normal cells which have been acted on by nonantigenic material Evidently it is possible to tie the various parts of the picture together

The incidence of allergy is always impressive, and one wonders whether the present high figures represent a fundamental change in the reaction of the population to modern life or whether they depend simply on the fact that physicians and laymen are becoming "allergy conscious" Service³ finds that major allergic diseases can be found in 20 per cent of the general population and that 16 per cent have more than one allergic symptom Norgaard⁴ writes that in Denmark about 200,000 patients with bronchial asthma are invalided each year, in a country which has a population of only 3,500,000 In other words,

1 Rackemann, F M Allergy Review of Literature of 1938, Arch Int Med **63**:173 (Jan) 1939

2 Dragstedt, C A Anaphylaxis and Allergy, Ann Int Med **13**:248, 1939

3 Service, W C The Incidence of Major Allergic Diseases in Colorado Springs, J A M A **112**:2034 (May 20) 1939

4 Norgaard, A Die soziale Bedeutung von Asthma bronchiale und eine Untersuchung des Nutzens bei einer Veränderung von Erwerb und Wohnort, Acta med Scandinav, 1938, supp 89, p 113

something over 5 per cent of the population suffers from asthma alone, and nothing is said about hay fever, eczema or urticaria. Less alarming, however, are the low figures of Stoesser and Shaperman⁵. In a total of 2,771 new admissions to the clinic in Minneapolis in a period of two years, there were only 141 cases of allergy, or 5 per cent. All of these figures are interesting, but they and others like them vary widely according to many circumstances hard to control, and the plain fact is that allergic diseases are very common and so are worthy of careful consideration.

ANAPHYLAXIS

As I have emphasized in previous reviews, the difference between the guinea pig and the rat is striking. The former is easy to sensitize, the latter is hard to sensitize. In the meantime, the Kopeloffs⁶ produced anaphylaxis in the monkey easily, first with horse serum and then with egg white. Precipitins, the Arthus phenomenon and typical Dale-Schultz reaction were all described in the treated monkeys. The "alarm reaction," so disconcerting to the demonstration of anaphylactic shock in the guinea pig, is described by Karady and his associates⁷. When the sensitized pigs were treated with formaldehyde, or were cooled to a temperature of 1 C for five hours or were made to walk in revolving cages, they became resistant to the subsequent shock. They survived the reinjection which killed all of the controls. Evidently, the preceding treatment had served to increase the resistance, obviously in some nonspecific manner, and the observation can be correlated no doubt with the important clinical experience that rough treatment of various kinds, notably fever and surgical operation, as well as full etherization, has a markedly beneficial, though temporary, effect on the course of human asthma. The recognition of the "alarm reaction" is timely. Another animal experiment is that of Molomut,⁸ who found that removal of the hypophysis from a rat can be accomplished with reasonable ease and renders the animal so treated subject to fatal anaphylactic shock without causing any change in the production of circulating antibodies.

5 Stoesser, A. V., and Shaperman, E. The Care of the Allergic Child, *Minnesota Med* **18** 292, 1935.

6 Kopeloff, L. M., and Kopeloff, N. Anaphylaxis in the Rhesus Monkey I. Horse Serum as an Antigen, *J. Immunol* **36** 83, 1939, II. Egg White as an Antigen, *ibid* **36** 101, 1939.

7 Karady, I., Selye, H., and Browne, J. S. L. The Influence of the Alarm Reaction on the Development of Anaphylactic Shock, *Orvosi hetil* **82** 681, 1938, abstracted, *J. Immunol* **35** 335, 1938.

8 Molomut, N. The Effect of Hypophysectomy on Immunity and Hypersensitivity in Rats with a Brief Description of the Operative Technic, *J. Immunol* **37** 113, 1939.

CHEMISTRY OF ALLERGY

A number of new reports show that the skin can be sensitized to a great variety of substances which are nonprotein and have relatively simple chemical structures. These will be discussed later in the section on diseases of the skin. Here, however, must be mentioned one or two interesting papers. Newell and his associates⁹ report a study of the protein in the Prausnitz-Kustner antibody. The Tiselius apparatus consists of a U tube that contains the solution to be tested, and through it is passed an electric current. The different protein constituents move through the tube at different rates of speed until eventually they become separated. This separation is shown by changes in concentration which produce deflection in a beam of light and so make it possible to observe different bands or shadows in the light between the protein fractions. With this method, Newell found that the Prausnitz-Kustner antibody is all in that globulin fraction which was designated as gamma by Tiselius. This gamma globulin is an important constituent of the pseudoglobulin of serum, for other experiments have shown that most other antibodies, like precipitins and agglutinins, are contained in it. The point is that the Prausnitz-Kustner antibody is chemically analogous to other antibodies, for example, the antibody in antipneumococcus serum.

The chemistry of allergens is always important. Studies on ragweed will be described later under the subject of hay fever. In a comprehensive article, Weiss¹⁰ has indicated the close relationship between biologic action and chemical structure. In 1937, Nitti and his co-workers,¹¹ in Paris, pointed to the importance of the precise chemical structure of allergens, saying that guinea pigs could be sensitized regularly by paraphenylenediamine but not by the ortho or meta isomers. Furthermore, when the amino group was replaced by an acetyl or a hydroxyl group the sensitizing power was lost. Spies, Bernton and Stevens¹² have studied the chemistry of the cottonseed embryo. An extract in distilled water was boiled and the coagulant removed and discarded. The filtrate was centrifuged, and to it alcohol was added to a final concentration of 75 per cent. The sticky, dark-colored precipitate was then dissolved in distilled water and was found to give a good cutaneous

9 Newell, J. M., Sterling, A., Oxman, M. F., Burden, S. S., and Krejci, L. E. Electrophoretic Separation of the Antibody from Human Allergic Serum, *J. Allergy* **10** 513, 1939.

10 Weiss, S. Chemical Structure—Biological Action, Therapeutic Effect, *New England J. Med.* **220** 906, 1939.

11 Nitti, F., Bovet, D., and Depierre, F. Les phénomènes allergiques provoqués par certaines amines aromatiques, *Rev. d'immunol.* **3** 376, 1937.

12 Spies, J. R., Bernton, H. S., and Stevens, H. The Chemistry of Allergens. Isolation of Active Fraction from Cottonseed, *J. Allergy* **10** 113, 1939.

reaction. Later, however, it was purified further by treatment with basic lead acetate and alcohol, which resulted in another precipitate. From this second filtrate the lead salts were removed by hydrogen sulfide, and the final material was precipitated by another treatment with 75 per cent alcohol. This second alcohol precipitate was dried and later taken up in water to make the solution several times as active as the original alcohol precipitate. It gave a Molisch reaction to carbohydrate and on hydrolysis a positive reaction with Benedict's solution. Treatment with trinitrophenol caused a heavy precipitate which gave negative reactions for carbohydrate. Solutions of this precipitate, however, produced cutaneous reactions which were quite as large as those with the original purified material. The authors attribute the allergenic properties to the protein rather than to the carbohydrate components.

Meantime, Abramson, Sookne and Moyer¹³ present a complicated study of electrical properties of ragweed, the results of which indicate that the "skin-reactive" constituent is protein-like in nature and that its isoelectric point lies between p_H 3.9 and p_H 4.3. An important contribution to the chemistry of allergy is the observation of Winkenwerder, Buell and Howard¹⁴ that patients with skin sensitivity to ragweed also give positive cutaneous reactions to the nucleic acids and their derivatives, including the crystalline nucleotides adenine, guanine and cytosine, and to simple purine salts like adenine sulfate, xanthine nitrate and sodium urate. Severe constitutional reactions were produced in 2 patients with doses as small as 0.02 mg. of adenine nucleotide. The fact that only an occasional reaction to these substances was observed in a group of 40 normal persons leads to the interesting query: Does ragweed contain nucleic acid, and if so are the cutaneous reactions to ragweed dependent on the nucleic acid component?

IMMUNOLOGY

The mechanism of the so-called desensitization treatment of hay fever has been studied further. It will be recalled that in 1935 Cooke, Barnard, Hebard and Stull¹⁵ injected mixtures of ragweed and ragweed-sensitive serum into the skin of normal persons. When the serum was obtained before treatment, the antibody in this A serum was neutralized by the ragweed. The mixture produced a one hour reaction, but it

13 Abramson, H. A., Sookne, A. M., and Moyer, L. S. Electrokinetic Phenomena. The Inactivation of Ragweed Pollen Extracts by Adsorption and the Electric Charge of the Resultant Surface, *J. Allergy* **10** 317, 1939.

14 Winkenwerder, W. L., Buell, M. V., and Howard, J. E. Preliminary Studies on the Sensitizing Properties of the Nucleic Acids and Their Derivatives, *Science* **90** 356, 1939.

15 Cooke, R. A., Barnard, J. H., Hebard, S., and Stull, A. Serological Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), *J. Exper. Med.* **62** 733, 1935.

failed to transfer the ragweed sensitiveness to the skin of a normal recipient. With the P serum obtained after treatment, on the other hand, there was no immediate reaction and yet passive transfer was successful. The authors concluded that in the second case there had developed a new mechanism by which the reaction between the allergen ragweed and the passive transfer antibody, the "reagin," had been inhibited. A new inhibiting antibody was described. This work has been confirmed by Harley,¹⁶ in England, and more recently by Langner and Kern.¹⁷ Incidentally, Harley found that if after a few days the sites in the recipient's skin were tested with ragweed again, the reaction then became positive, thus showing that the attachment of the reaction-inhibiting substance to the antibody was not stable. In a later paper, Cooke, Loveless and Stull¹⁸ found that volunteers who had been treated repeatedly with mixtures of ragweed extract and ragweed-sensitive serum failed to show any serologic changes. In another group, however, larger amounts of ragweed without sensitive serum were given, and in this group serologic changes did occur and were found to be similar to those observed in the ragweed-sensitive patients after successful treatment, that is, there were inhibition of the immediate reaction and successful passive transfer. The combination of the sensitive serum and the ragweed was inhibited, and by a factor which was later found to occur in the pseudoglobulin, no doubt the gamma globulin fraction of the serum already discussed. Langner and Kern¹⁷ repeated the experiment with precisely the same technic and obtained precisely the same results. In addition, these authors describe a new form of treatment. They obtained serum from patients with hay fever who had been treated successfully by the ordinary method and dried it by the so-called lyophile process—a rapid freezing and dehydration *in vacuo* at low pressure. This dried serum was then taken up in half the original quantity of water and was injected intramuscularly into patients with active symptoms. Moderate malaise often resulted, but the relief from hay fever was complete in 9 of 11 patients. However, in 3 patients the relief did not continue for longer than a week. To control their experiments, the authors injected normal serum treated in the same manner but obtained no results. More recently, Sherman and Stull¹⁹ studied the serum

16 Harley, D. Hay Fever. Effect of Pollen Therapy on Skin Reactions, Reaction-Inhibiting Substance in Serum of Treated Patients, *J. Path. & Bact.* **44** 589, 1937.

17 Langner, P. H., and Kern, R. A. Studies on the Immunology of Hay Fever, *J. Allergy* **10**:1, 1938.

18 Cooke, R. A., Loveless, M., and Stull, A. Studies on Immunity in Type of Human Allergy (Hay Fever). Serologic Response of Nonsensitive Individuals to Pollen Injections, *J. Exper. Med.* **66** 689, 1937.

19 Sherman, W. B., and Stull, A. Serological Changes Resulting from the Treatment of Hay Fever Over a Period of Years, *J. Allergy* **10** 465, 1939.

of 55 patients at the end of their treatment. Passive transfer failed entirely in 9 of them, and the response was weak in 30 others. Of the 29 untreated patients, however, 22 showed good transfers. Furthermore, it was found that with successive years of treatment there was a qualitative change in the character of the antibody. The ability to transfer sensitiveness diminished, while the ability to neutralize the ragweed increased. Schmidt and Lippard²⁰ also studied the effect of pollen treatment on the concentration of the passive transfer antibody. Constant amounts of serum were incubated with different amounts of antigen, and the mixtures were used to sensitize the recipients' skin. The more antigen that was required to neutralize the antibody and so to prevent the passive transfer reaction, the stronger was the serum. They found that the titer increased after treatment, but with no particular relation to the amount of treatment, that is, to the largest dose tolerated. In many cases, the titer rose to more than tenfold its pretreatment level. In another paper, Lippard and Schmidt²¹ studied the changes in antibody (reagin) titer which occurred in children sensitive to a food after the ingestion of that food. They found that there was an increase but that it varied in amount. This increase seemed to indicate that the rising titer of antibody was a protective mechanism, and it was in accord with the observation that after the first feeding the children could take the same food with less clinical difficulty.

Several papers concern the transfer of anaphylactic sensitiveness from animals to the human skin. First, Eagle, Arbesman and Winkenwerder²² have reviewed the literature and reopened the question of the antigenicity of ragweed in animals. Using four types of extract of short ragweed pollen without preliminary alum precipitation and without the use of adjuvant antigens, they found that fatal anaphylaxis could be produced regularly in guinea pigs by both active and passive sensitization and that precipitating and complement-fixing antibodies could be produced in high titer in rabbits. (In their extracts, the total nitrogen varied between 0.60 and 1.05 mg per cubic centimeter.) In the following paper²³ they showed that some of the rabbit antisera

20 Schmidt, W. M., and Lippard, V. W. Human Passive Transfer Antibody. III. Serial Titrations on Treated and Untreated Patients with Hay Fever, *Am J Dis Child* **56** 550 (Sept.) 1938.

21 Lippard, V. W., and Schmidt, W. M. Human Passive Transfer Antibody. IV. Studies on Children Hypersensitive to Foods, *Am J Dis Child* **56** 797 (Oct.) 1938.

22 Eagle, H., Arbesman, C. E., and Winkenwerder, W. L. The Production in Experimental Animals of Antibodies to Short-Ragweed Pollen (Precipitation, Complement-Fixation, and Anaphylaxis), *J Immunol* **36** 425, 1939.

23 Winkenwerder, W. L., Eagle, H., and Arbesman, C. E. On the Presence in Rabbit Antisera vs Ragweed Pollen of Skin-Sensitizing Antibodies Passively Transferable to Man, *J Immunol* **36** 435, 1939.

were capable of transferring the sensitiveness to the human skin. However, the transfer ability was not parallel with the precipitin content. Sherman, Stull and Hampton²⁴ made a similar experiment on guinea pigs and found that the serum from half their animals could sensitize human skin without difficulty, but that the intensity of the subsequent test reaction was not as great as that produced by the serums of acutely sensitive human beings.

SERUM DISEASE

This year there are a number of reports which call attention to the involvement of the nervous system in serum disease. Neuritis is not an uncommon sequel. It develops apparently from compression of the nerves by the perineural edema. Bennett²⁵ has made a careful study of the literature and adds 5 cases. Hoagland²⁶ and Meszaros²⁷ each observed a case. Iritis is reported by Theodore and Lewson²⁸. Finally, cerebral manifestations, including loss of consciousness, aphasia and partial paralysis, are described in papers by Lemierre²⁹ and by Kennedy and his associates³⁰.

Abdominal symptoms may complicate serum sickness. Clog³¹ reports a case in which surgical intervention revealed swelling of the mesenteric glands and marked hyperemia of the peritoneum.

Various treatments for serum disease have been advised. Voss and Hundt³² used convalescent serum from patients recently recovered from serum disease, and in so doing made an interesting observation.

24 Sherman, W. B., Stull, A., and Hampton, S. F. Passive Sensitization of Human Skin by Serum of Experimentally Sensitized Animals, *J. Immunol.* **36** 447, 1939.

25 Bennett, A. E. Horse Serum Neuritis, with Report of Five Cases, *J. A. M. A.* **112**:590 (Feb. 18) 1939.

26 Hoagland, R. J. Neuritis Following Serum Administration, *Mil. Surgeon* **82** 134, 1938.

27 Meszaros, K. Durch Tetanusschutzimpfung verursachte Neuritis, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **30** 45, 1938.

28 Theodore, F. H., and Lewson, A. C. Bilateral Iritis Complicating Serum Sickness, *Arch. Ophthalmol.* **21** 828 (May) 1939.

29 Lemierre, A. Un cas de manifestations cérébrales de la maladie sérique, *Bull. et mém. Soc. méd. d. hôp. de Paris* **54** 827, 1938.

30 Kennedy, F., Wortis, S. B., and Wortis, H. Clinical Evidence for Cerebral Vasomotor Changes, *New York State J. Med.* **38** 1441, 1938.

31 Clog, M. L. Syndromes douloureux abdominaux au cours de la maladie sérique, *Bull. Soc. pédiat. de Paris* **36** 354, 1938.

32 Voss, E. A., and Hundt, O. Das Prinzip der inversen Anaphylaxie als Methode des Antikörpernachweises beim Menschen, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **94** 281, 1938. Voss, E. A. Inverse Anaphylaxie beim Menschen zugleich ein Beitrag zur Problematik der Ueberempfindlichkeitserscheinungen beim Menschen, *Ztschr. f. Kinderh.* **59** 612, 1938.

When this serum, full of antibodies for horse serum, is injected into a child several days after a dose of horse serum, interesting reactions occur which the authors describe as "inverse" anaphylaxis and which increase in severity as the time of treatment after the original dose of horse serum becomes longer. If the convalescent human serum is given within the first three days, a small wheal and erythema appear at the site of injection of the horse serum, but if given after the fourth day, the local wheal spreads to a general rash. If the convalescent serum is delayed until the eighth or ninth day, a general shocklike reaction may result. However, when these reactions have subsided, the serum disease improves. One should note, however, that the course of serum disease is usually short anyway.

Histaminase will be discussed later. Meantime, Foshay and Hagebusch³³ have used it in treatment of serum disease and have found it helpful. Eight patients were given the tablets by mouth and 6 were relieved in from seven to thirty-six hours. Twelve patients were treated with intramuscular doses of histaminase and 11 were relieved. For prophylaxis, the authors recommend that 4 or 5 tablets containing 5 units each be given three times a day, beginning at the time of injection of the prophylactic serum.

An interesting observation is that of Fleisher and Jones,³⁴ who found that the addition of sodium hydroxide to serum, followed by warming to 55 C and subsequent neutralization, prevented the development of serum disease in rabbits. Unfortunately, the preparations were toxic for many animals, and so the method can hardly be applied to the prevention or treatment of serum disease in man.

HAY FEVER

New pollen surveys are reported by Deamer and his associates³⁵ for the country north of San Francisco, by Cole³⁶ for Ames, Iowa, and by Metzger³⁷ for the west coast of Florida. There is little ragweed in Florida.

33 Foshay, L, and Hagebusch, O E. Histaminase in the Treatment of Serum Sickness, *J A M A* **112** 2398 (June 10) 1939.

34 Fleisher, M S, and Jones, L R. Serum Sickness in Rabbits. VII. A Method for Removing or Destroying the Factor Causing Serum Sickness, *J Immunol* **36** 511, 1939.

35 Deamer, W C, Jenkins, H L, and Lazarus, D S. Pollen Survey Report on Arcata District, Humboldt County, California, *California & West Med* **49** 450, 1938.

36 Cole, J A. Pollen Survey in Ames, Iowa, in 1938, *J Iowa M Soc* **29** 198, 1939.

37 Metzger, F C. The Climatic Treatment of Hay Fever and Asthma, with Special Reference to Florida, *J A M A* **112** 29 (Jan 7) 1939.

The antigenic relationships of different pollens have been studied further. Hampton, Stull and Cooke³⁸ tested the uterus of guinea pigs sensitized to alum-precipitated ragweed for reactions to other pollens at the same time. Uterine strips which reacted to the specific pollen with a large contraction reacted to the related pollen in 17 of 38 tests. In other words, the experiment indicated an antigenic relationship, but not identity, of the pollens used. The authors worked not only with the low and giant ragweeds but with the three common grasses timothy, orchard grass and June grass as well. With a different technique, Prince and Secrest³⁹ studied the relations between ragweed and marsh elder. Using the serum of patients sensitive to both weeds, they passively sensitized sites on the skin of normal recipients and then desensitized these sites by treatment, first with ragweed and then with marsh elder pollen. When the sites were exhausted with ragweed, they still responded to marsh elder, but when exhausted with marsh elder they were exhausted for ragweed at the same time. Here again was a close, though not absolute, relationship.

Another sort of investigation concerns the standardization of pollen extracts—the determination of their potency. Arbesman and Eagle⁴⁰ point out that each of the present methods for the assay of extracts is open to criticism and that true values must wait for an adequate chemical identification of the active principle. They describe the variables concerned in the experiments of passive transfer, which are many and difficult to control.

Stull and Sherman⁴¹ present further evidence to support Cooke's finding that the allergenic strength of pollen extracts depends primarily on the content of protein nitrogen.

The treatment of hay fever has been discussed this year chiefly in relation to oral therapy. Zeller⁴² reviews the history. In 1922 Touart treated 6 patients with good results, and in the same year Solomon had similar experiences. In 1927 Black showed that ragweed antigen could

38 Hampton, S. F., Stull, A., and Cooke, R. A. Antigenic Studies by the Dale Test. I. The Antigenic Relationship of Certain Pollens, *J. Allergy* **10** 417, 1939.

39 Prince, H. E., and Secrest, P. G., Jr. Immunological Relationship of Giant, Western, Common Ragweed and Marsh Elder (*Iva ciliata*), *J. Allergy* **10** 537, 1939.

40 Arbesman, C. E., and Eagle, H. The Assay of Ragweed Pollen Extracts, *J. Allergy* **10** 521, 1939.

41 Stull, A., and Sherman, W. B. Further Studies on the Allergenic Activity of Protein and Nonprotein Nitrogen Fractions of Ragweed Pollen Extract, *J. Allergy* **10**:130, 1939.

42 Zeller, M. Oral Ragweed Pollen Therapy, *J. Allergy* **10** 579, 1939.

be demonstrated in the blood stream and urine after the taking of pollen by mouth, and in 1928 his report on the oral treatment of 71 patients was enthusiastic. In 1929 he was less enthusiastic. Now, in 1939, Black⁴³ has treated 40 patients, who were sensitive to ragweed and who applied for treatment during the week before the onset of the hay fever season, with doses of the dried pollen by mouth. Good results, however, were obtained in only 12 patients, or 40 per cent—a low figure. It is interesting that as soon as the oral treatment was started, Black noted that the hypodermic doses could be increased without causing the large local reactions observed before the oral doses had been given. Other reports on oral treatment are conflicting. Rockwell⁴⁴ treated 182 patients, with good results in 63 per cent. Bernstein and Feinberg,⁴⁵ however, treated 20 patients coseasonally, with good results in only 2. The discussion of Zeller's paper, which was read before the Association for the Study of Allergy in May 1939, was particularly interesting, for it concerned chiefly the question of absorption of the ingested pollen. The chief evidence for absorption is the immediate reaction which occurs in the skin of ragweed-sensitive patients when the serum drawn from a patient soon after the taking of pollen by mouth is injected into it. As Feinberg said, human serum of many types causes immediate reactions which are hard to interpret, but at least they are non-specific. However, as Black said in his discussion, "It seems inconsistent to say that the antigen is not absorbed and then to say that the patient developed asthma and hay fever as the result of the absorption." Whereas the whole subject is controversial, the evidence so far indicates that oral therapy is not beneficial, and so the Chicago Society of Allergy has urged that the commercial promotion of oral pollen therapy should be deferred in the interest of the public and the general practitioner until further experimentation now in progress has been reported.

Meantime, the constitutional reactions which constitute a great danger in pollen therapy have been studied by Greene,⁴⁶ who has reviewed the literature and analyzed the cases in the series which he and I have studied.

43 Black, J. H. The Oral Administration of Ragweed Pollen, *J. Allergy* **10** 156, 1939.

44 Rockwell, G. E. Clinical Results in the Prevention and Treatment of Hay Fever by Oral Administration of Pollens of the Grass and Ragweed Types, *Ohio State M. J.* **34** 784, 1938.

45 Bernstein, T. B., and Feinberg, S. M. Oral Ragweed Pollen Therapy. Clinical Results of Experiments on Gastro-Intestinal Absorption, *Arch. Int. Med.* **62** 297 (Aug.) 1938.

46 Greene, J. E. Constitutional Reactions in Hay Fever Therapy, *M. Clin. North America* **23** 1255, 1939.

FUNGOUS SPORES

Durham⁴⁷ presents further information on the high incidence of airborne fungous spores in this country. Pratt⁴⁸ has made a careful study of the mold spores in the air of Boston. He exposed Petri dishes out of doors for a half-hour each day for a year and found that *Alternaria*, *Hormodendrum* and non-spore-bearing molds increase in summer while *Aspergillus* and *Penicillium* have no seasonal incidence. In his experience, these molds are of considerable practical importance, for 25 per cent of 177 children with seasonal asthma and hay fever reacted to *Alternaria* in cutaneous and passive transfer tests, and when they were treated with this mold, with and sometimes even without pollen treatment at the same time, the results were good.

Grain smuts and rusts are emphasized by Wittich,⁴⁹ who found them to be the principal cause of trouble in 8 cases. Harris⁵⁰ reported 13 cases of the same sort. The patients gave a history of hay fever or asthma in the presence of the grain smuts. Furthermore, Harris was able to reproduce the symptoms by instilling the grain dust or the smuts into the patient's nostril. In another paper, Harris⁵¹ reported that whereas the common molds, like *Alternaria*, bore no antigenic relationship to extracts of wheat or oat, nevertheless wheat smuts could be neutralized by wheat dust and vice versa, the technic being that of the ordinary desensitization of passively sensitized skin sites. Meantime, Henrici⁵² found that *Aspergillus fumigatus* contains an endotoxin poisonous for guinea pigs. When an extract from the finely ground mycelium mass was injected subcutaneously, there developed massive edema with necrosis and ulceration, and when it was given intravenously, it caused fatty changes in the liver and necrosis of the kidney tubules as well as hemolysis. This study was made on guinea pigs, but it goes to show that not all of the mold extracts can be used with impunity.

VASOMOTOR RHINITIS

Chronic vasomotor rhinitis, with the pale, boggy swelling of the nasal mucous membrane and symptoms which are very troublesome

47 Durham, O. C. Incidence of Air-Borne Fungus Spores. II. *Hormodendrum*, *Alternaria* and Rust Spores, *J. Allergy* **10**:40, 1938, An Unusual Shower of Fungus Spores, *J. A. M. A.* **111**:24 (July 2) 1938.

48 Pratt, H. N. Mold Spore Content of the Air in Boston, with Reference to Atopic Sensitivity, *J. Pediat.* **14**:234, 1939.

49 Wittich, F. W. Further Observations on Allergy to Smuts. *Journal-Lancet* **59**:382, 1939.

50 Harris, L. H. Allergy to Grain Dusts and Smuts, *J. Allergy* **10**:327, 1939.

51 Harris, L. H. The Nature of the Grain Dust Antigen. Crossed Reactions to Grain Dusts and Smuts, *J. Allergy* **10**:433, 1939.

52 Henrici, A. T. An Endotoxin from *Aspergillus Fumigatus*, *J. Immunol.* **36**:319, 1939.

because of their persistence, needs much further study Winkenwerder and Gay⁵³ have analyzed 198 cases and found that house dust, feathers and orris powder were responsible in 95 per cent, with infections of the sinuses important in only 22 cases (11 per cent) In a rather stormy article, Piness and Miller⁵⁴ object to the indiscriminate removal of tonsils from those children who suffer from repeated colds and bronchitis and who have allergy as the essential cause of their trouble A million and a half tonsillectomies are performed in the United States each year, and the operation seems to have little effect on the subsequent development of hay fever or asthma, for the figures for the development of allergy are the same for the group with tonsillectomy as for the group with the tonsils still in place

Meantime, Hoseason,⁵⁵ in England, has an interesting observation on vasomotor rhinorrhea with asthma, saying that nasal congestion is one of the specific cutaneous responses to the estrogens which circulate during estrus The rhinorrhea is apt to be worse immediately before menstruation, and asthma may supervene at that time Treatment, however, is not discussed except to say that zinc ionization is the simplest and most effective method Another English report is that of Wilson-Pepper and Royle,⁵⁶ who found that one injection of progesterone, the corpus luteum hormone, controlled the symptoms in a woman who suffered from menorrhagia and marked spasmodic rhinorrhea

ASTHMA

Asthma is usually due to allergy In most cases, a careful history will reveal the nature of the causative factor In diagnosis, cutaneous tests are important, and several papers appear on them It always seems curious to me that whereas many men test their patients with hundreds of substances, including many foods, reports on the results of tests with foods are unusual and deal chiefly with the more common articles—eggs, wheat, milk and fish Dusts, on the other hand, are of great practical importance as a cause of asthma in adults (much greater than foods), and so one finds references to a wide range of pollens, to the animal danders, to a variety of occupational dusts and to a number of

53 Winkenwerder, W L, and Gay, L N Perennial Allergic Rhinitis An Analysis of One Hundred and Ninety-Eight Cases, *Bull Johns Hopkins Hosp* **61** 90, 1937

54 Piness, G, and Miller, H Allergy of the Upper Respiratory Tract in Infancy and Childhood, *J A M A* **113** 734 (Aug 19) 1939

55 Hoseason, A S Vasomotor Rhinorrhea, with Asthma, Associated with Menstruation, *Brit M J* **2** 703, 1938

56 Wilson-Pepper, J K, and Royle, H Progesterone and the Nasal Mucosa, *Brit M J* **1** 974, 1939

materials in household furniture Withers' ⁵⁷ paper is therefore of interest He studied 20 patients clinically sensitive to one or more foods, including, besides the cereals, the bean and tomato families He found 91 patients with positive clinical sensitiveness, and yet only half of these had accompanying positive cutaneous reactions On the other hand, of 65 patients with negative clinical reactions, 31 had positive cutaneous reactions—again nearly half His evidence makes it clear that clinical observations are much more satisfactory than are the direct or the indirect method of testing

Cow's milk is one of the important items Although his latest paper is not yet published, Hill's ⁵⁸ studies on milk are significant When a normal infant first drinks cow's milk, precipitins develop in the blood in ten days, and also there is a positive reaction to the intracutaneous test for milk, though never to the scratch test After two to three weeks, however, the cutaneous reaction fades, while the circulating antibodies, precipitins and complement-fixing bodies continue for many months and then slowly disappear Allergy to milk shows itself in reactions of three kinds The first and most common is eczema, with its typical distribution on the face, neck and cubital and popliteal spaces It is properly called "atopic eczema" Sixty per cent of babies with eczema give positive responses to lactalbumin, while only 17 per cent react to casein at the same time The last observation explains the fact that the substitution of goat's milk is not always followed by clearing of the eczema, for goat casein is the same as cow casein Milk is really two foods instead of one, and the fact is not ordinarily recognized The second type of reaction to milk consists of gastrointestinal symptoms, with or without asthma at the same time Colic and pylorospasm are said to be due to milk in rare cases The third type of reaction is also rare and consists of an anaphylactic-like shock which occurs when the breast-fed baby is given his first feeding of cow's milk The time interval is probably a deciding factor in the character of the reaction The baby with eczema has, on the chances, taken a quart (about 950 cc) of milk every day, whereas the baby who reacts with shock had trouble on the first feeding of milk From Scandinavia comes a similar series of observations by von Sydow ⁵⁹ He recognized a group of infants who reacted to milk with eczema and asthma and were not amenable to desensitization and another group with gastrointestinal symptoms who subsequently did acquire tolerance to milk

⁵⁷ Withers, O R Food Allergens II Atopic Reagents and the Botanical Classification of Foods, *J Allergy* **10** 105, 1939

⁵⁸ Hill, L W Milk as an Allergen, personal communication to the author

⁵⁹ von Sydow, G Some Cases of "Cow's Milk Idiosyncrasy" *Acta pædiat* **23**:383, 1939

The old question of the difference between raw food and cooked food in the production of symptoms, and also as the source of cutaneous test material, has been aired. On the one hand, Ratner and Gruehl⁶⁰ found that guinea pigs given injections of raw cereal products show a high sensitivity, whereas heating destroys the sensitizing power. On the other hand, Malkin and Markow,⁶¹ in their clinic, made cutaneous tests with raw and with cooked foods side by side and found that in 92 per cent of their cases the reactions were the same. It is tempting to doubt whether any of their reactions were of clinical significance.

Tobacco presents an interesting problem, with various authors holding different points of view. It is interesting that Peshkin and Landay⁶² have found that the cutaneous reaction to tobacco occurs more commonly in patients who are sensitive to pollen, either of grass or of ragweed. Harkavy⁶³ reviews the recent literature.

INTRINSIC ASTHMA

Last spring, at the meeting of the Association for the Study of Allergy in St. Louis, I⁶⁴ pointed out that "all is not allergy that wheezes," and on the same program was a paper by Alexander,⁶⁵ entitled "Allergic Syndromes in the Absence of Allergens." If all the cases of asthma are studied together, it appears that in about 25 per cent of them a careful history will not reveal a possible relation to diet or environment. In the relatively clean environment of the hospital, even in an oxygen tent, the asthma continues. Furthermore, the deaths from asthma which I have observed have occurred only in this group with intrinsic asthma. Of 283 patients, 20 have died of asthma—a proportion of 8.2 per cent. In this group with intrinsic asthma the cause of trouble is much in doubt. Clinical experience suggests that the symptoms be designated as part of an "asthma syndrome" rather than as mere "asthma," for with the asthma in these cases go several rather characteristic features. Diseases of the paranasal sinuses occur in at least three fourths of the cases, in most of which operations on sinuses have already been done, without

60 Ratner, B., and Gruehl, H. L. Anaphylactogenic Properties of Certain Cereal Foods and Breadstuffs, Allergenic Denaturation by Heat, *Am J Dis Child* **57** 739 (April) 1939.

61 Malkin, J. I., and Markow, H. An Analysis of the Comparative Results of Skin Testing with Cooked and Uncooked Foods. Preliminary Report, *J Allergy* **10** 337, 1939.

62 Peshkin, M. M., and Landay, L. H. Cutaneous Reactions to Tobacco Antigen in Allergic and in Non-Allergic Children, with Direct and Indirect (Local Passive Transfer) Methods of Testing, *Am J Dis Child* **57** 1288 (June) 1939.

63 Harkavy, J. Tobacco Skin Reactions and Their Clinical Significance, *J Invest Dermat* **2** 257, 1939.

64 Rackemann, F. M. Intrinsic Asthma, *J Allergy*, to be published.

65 Alexander, H. L. Allergic Syndromes in the Absence of Allergens, read before the Society for the Study of Allergy, St. Louis, May 16, 1939.

benefit to the asthma. Eosinophilia is characteristic. Malaise is prominent (Vaughan has called it "allergic toxemia"). Finally, Greene and I⁶⁶ have reported on an interesting subgroup of patients with asthma who were found to suffer also from periarteritis nodosa. It becomes important, therefore, to study the physiology of asthma and to learn about other conditions which are accompanied by the symptom of wheezing. In the fatal cases in our series, autopsy showed two types of lesion. In 18 instances the bronchi were filled with tough, sticky plugs, sufficient to cause death by suffocation. In the other 2 cases, however, plugs were not observed, and the lungs were not so distended, the cause of death was evidently concerned with a physiologic or functional spasm of the muscles in the smaller bronchi rather than with obvious mechanical plugging of their lumen.

Prickman and Moersch⁶⁷ have had wide experience with bronchoscopy in treatment of asthma. Of 83 consecutive asthmatic patients, they found stenosis of one or more of the bronchi in 40 per cent. Balyeat and Seyler⁶⁸ say that in severe asthma there are two factors, one being sensitization, the other a chemical factor, and that the symptoms depend on local edema of the mucosa of the bronchial tubes, which in turn depends on a chronic infection. The trouble with the infectious theory is that, in my cases at least, absence of any pathologic evidence of infection was one of the striking features.

Friedman and Molony⁶⁹ comment on the role of allergy in atelectasis and describe 6 cases in which plugs producing bronchial occlusion could be removed through the bronchoscope, with great benefit. They found that the occlusions were due to allergy. On the other hand, Schneider⁷⁰ describes a case of a 9 month old child who had occlusion of a bronchus from pressure of tuberculous lymph nodes and whose condition had been diagnosed erroneously as bronchial asthma. In many of our patients who died of intrinsic asthma local areas of collapse were observed at autopsy, and it is surprising that the complication does not occur, or at least is not recognized, more often. If masses of sticky mucus can plug the bronchi partially by a ball valve mechanism to produce emphysema, it is easy to believe that they can also plug them completely.

66 Rackemann, F. M., and Greene, J. C. Periarteritis Nodosa and Asthma, *Tr. A. Am. Physicians* **54** 112, 1939.

67 Prickman, L. E., and Moersch, H. J. Asthma and Its Association with Bronchostenosis, *M. Clin. North America* **23**:961, 1939.

68 Balyeat, R. M., and Seyler, L. E. Dual Etiology of Intractable Asthma, *J. Oklahoma M. A.* **32** 49, 1939.

69 Friedman, T. B., and Molony, C. J. Role of Allergy in Atelectasis in Children, *Am. J. Dis. Child.* **58** 237 (Aug.) 1939.

70 Schneider, L. V. Bronchial Occlusion Due to Tuberculous Lymphadenitis, *Am. Rev. Tuberc.* **38** 320, 1938.

to produce atelectasis, if the argument is carried a bit further, one can understand how the atelectasis may lead to bronchiectasis

Watson and Kibler⁷¹ studied 46 cases of bronchiectasis and found sinusitis in 67 per cent and asthma in 32 per cent. Their statement that "the common association of sinusitis and bronchitis can be explained on the basis of allergy" is interesting and is comparable with the earlier suggestion of Kern and Schenck⁷² that nasal polyps were of allergic origin. In both instances I agree with the premises, but I should like to substitute the term "asthma syndrome" for that of "allergy."

In 1932, Loeffler⁷³ described local infiltrations, *Fruhinfiltrate*, which were found by roentgen examination in patients, usually children, suffering from mild respiratory symptoms. The patients were not sick, and the lesions were found to clear usually within a few weeks. The eosinophils in the blood were increased, often to 10 per cent, but the author said nothing of asthma. Tuberculosis, tumor and abscess could each be excluded in the differential diagnosis. This year there are four reports⁷⁴ on "Loeffler's syndrome" (by Breton, Cohen, Soederling and Weber, respectively), and each of them suggests that the cause is allergy. These reports fit well the conception of local atelectasis due to bronchial occlusion as a transient process, dense enough to cast a shadow in the roentgenogram, and evidently much more common than has been appreciated. Evidently, too, the process can occur even in cases of relatively mild asthma, for the reports available do not emphasize the life and death struggle which I have seen in the hospital.

According to Cole and Cole,⁷⁵ silicosis is accompanied by dyspnea, often simulating asthma. Here, however, the symptoms depend on capillary occlusion which involves large localized areas of the lung, accompanied by compensatory capillary dilatation in other regions.

71 Watson, S. H., and Kibler, C. S. The Role of Allergy in Bronchiectasis, *J. Allergy* **10** 364, 1939.

72 Kern, R. A., and Schenck, H. P. Importance of Allergy in Etiology and Treatment of Nasal Mucous Polyps, *J. A. M. A.* **103** 1293 (Oct 2) 1934.

73 Loeffler, W. Zur Differential-Diagnose der Lungeninfiltrationen. I. Fruhinfiltrate unter besonderer Berücksichtigung der Rückbildungszeiten, *Beitr. z. Klin. d. Tuberk.* **79** 338, 1932, II. Ueber fluchtige Succedan-Infiltrate (mit Eosinophilie), *ibid.* **79** 368, 1932.

74 Breton, A. A propos de la radiologie de l'asthme. Le syndrome de Loeffler, *Paris méd.* **1** 538, 1938. Cohen, R. Le syndrome de Loeffler (Infiltrations pulmonaires fugaces avec eosinophilie), *Presse méd.* **46** 797, 1938. Soederling, B. Transient Lung Consolidations in Asthmatic Children with Reference to Eosinophilia, *Arch. Dis. Childhood* **14** 22, 1939. Weber, F. P. Transient Pulmonary Infiltration with Blood Eosinophilia (Loeffler's Syndrome), *Brit. J. Child. Dis.* **36** 15, 1939.

75 Cole, L. G., and Cole, W. G. Dyspnea of Silicosis, *J. A. M. A.* **113** 1216 (Sept 23) 1939.

Bilharzial asthma is another interesting disease which fits in with the conception that "all is not allergy that wheezes," the term "allergy" being used in the sense of hypersensitiveness to dusts or foods. Four cases have been presented by Mainzer⁷⁶. The disease is a schistosomiasis of the lungs. The spleen is large. There is fever, and the eosinophil count may be as high as 60 or 70 per cent, with high white cell counts. Roentgenograms show striations throughout the pulmonary fields. The treatment is easy, for when antimony is given the asthma clears and the eosinophils decrease. The author believes that the asthma is an allergic reaction to the products of the worms or their eggs and is not due to anatomic changes in the lung. These lesions persist long after the asthma has gone, and, furthermore, they are common whereas asthma is a rare complication of the disease.

Every one interested in asthma and in all questions pertaining to the pulmonary circulation should examine carefully the fascinating study of the pulmonary circulation by Robb and Steinberg⁷⁷. Diodrast is a chemical which contains approximately 50 per cent of iodine and which, being water soluble, has been used for intravenous pyelography. The authors have demonstrated that if roentgenograms of the chest are taken within a few seconds after the intravenous injection of diodrast, shadows of the various chambers of the heart and large blood vessels can be obtained. The reproductions of roentgenograms in their article are good enough to convey an excellent idea of the anatomy of these large vessels and something of their pathology.

Further information on the state of pulmonary circulation can be obtained by finding the circulation time. The method and the results are explained by Plotz,⁷⁸ who used the taste produced by intravenous injection of ether to measure the arm to lung time and the flush produced by intravenous administration of sodium cyanide to measure the arm to carotid time. The difference is the "left heart" time.

Cardiac asthma and the diseases of the pulmonary system of arteries, such as Ayerza's disease, which are often difficult to diagnose during life, should not be neglected in the list of conditions which can give rise to the symptom asthma. So also should be included emphysema. There is evidence not only that emphysema is a secondary development, resulting from chronic pulmonary disease, including asthma, but that "primary

76 Mainzer, F. Bilharzial Asthma. A New Type of Allergic Bronchial Asthma, *J. Allergy* **10** 349, 1939.

77 Robb, G. P., and Steinberg, I. Visualization of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease. A Case Study, *Ann Int Med* **13** 12, 1939.

78 Plotz, M. Asthmatic Heart Failure. A Form of Left Ventricular Failure and Its Differentiation from Bronchial Asthma by Circulation Time and Other Criteria, *Ann Int Med* **13** 151, 1939.

idiopathic emphysema" is a disease entity of considerable practical and theoretic importance. It is entirely proper to maintain that "all is not allergy that wheezes."

NOSE AND THROAT

Lesions of the nose and throat are common in asthma, as already stated. The recent literature has been well reviewed by Hansel,⁷⁹ but two papers deserve special attention. Francis and Stuart-Harris⁸⁰ infected ferrets with epidemic virus intranasally and then followed the progress of the disease by pathologic sections of the nasal mucous membrane of animals killed at various intervals. Their article is full of excellent pictures which show the development of the exudate, with sloughing of the whole surface on the second day and beginning of repair on the fourth day, and the changes in the character of the epithelium, culminating in the reestablishment of cilia on the tenth day. In a subsequent paper, they show that the epithelium in the process of repair and regeneration is unusually resistant to reinfection and physicochemical changes. Reinoculation with the virus produced only a structureless exudate, and ionization performed on the eighth day after infection caused little damage. Later, however, on the twenty-eighth day, ionization produced the usual severe reaction. The article is an excellent exposition of the manner in which the nasal mucosa behaves after injury. The second paper is one by Semenov⁸¹ on the surgical pathology of nasal disease. This paper, too, has many excellent photographs of pathologic specimens which demonstrate the various changes that lead to thickening of the membrane, formation of cysts, inclusion of small foci of infection and formation of polyps—a timely study.

Meantime, and somewhat against my theory that nasal lesions are a part of the picture and not a cause of it, are the 2 cases cited by Bourne⁸² in which injuries to the nasal septum were the precipitating factor in the production of asthma in predisposed persons. In both patients the asthma completely disappeared in one year and in two months, respectively, after submucous resection had been performed.

79 Hansel, F. K. Allergy as Related to Otolaryngology and Ophthalmology Literature for 1938, *J. Allergy* **10** 187, 1939.

80 Francis, T., Jr., and Stuart-Harris, C. H. Studies on the Nasal Histology of Epidemic Influenza Virus Infection in the Ferret. I. The Development and Repair of the Nasal Lesion, *J. Exper. Med.* **68** 789, 1938, II. The Resistance of Regenerating Respiratory Epithelium to Reinfection and to Physiochemical Injury, *ibid.* **68** 803, 1938.

81 Semenov, H. The Surgical Pathology of Nasal Sinusitis, *J. A. M. A.* **111** 2189 (Dec. 10) 1938.

82 Bourne, W. A. Asthma as a Sequel of Nasal Injury, *Brit. M. J.* **1** 870, 1939.

HISTAMINE

Interest continues in the theory that histamine may be the common denominator through which a variety of exciting causes can produce asthma. In his Bancroft Memorial Lecture, Kellaway,⁸³ of Australia, reviews the work on histamine as the effector set free by cellular injury. Recent titles under histamine in the *Quarterly Cumulative Index Medicus* indicate the many agents which can cause liberation of histamine: trypsin, curare, irritating vapors, fish poison, snake venom, anaphylactic shock and the Schwartzman reaction. Clinical studies on histamine are going on at the present time in at least five laboratories in this country. Unfortunately, the reports have not all appeared. The work is immensely difficult, chiefly because the amount of histamine present in the blood of patients with asthma is so small that it can be detected only by biologic methods, which are cumbersome and difficult. Abramson and Ochs⁸⁴ suggest that a modification of the ordinary cutaneous test to which histamine reacts promptly might give useful information. By using an electric current, they have been able to force histamine through the skin of man and animals and have found that by the method histamine can be detected in a concentration of less than 1/1,000,000. The article includes a number of interesting experiments in which a known quantity of histamine was added to the blood of rabbits and guinea pigs and could later be "recovered" with considerable accuracy. Evidently the method is sound as it is also simple. Farmer⁸⁵ has been able to treat guinea pigs with histamine in such a way that the uterine strip is insensitive to the amount of antigen (horse serum) that causes a good contraction in untreated controls. Furthermore, the histamine treatment renders the strip less sensitive to histamine itself, and so in another paper⁸⁶ he calls the effect desensitization. He observed it also when the guinea pigs were given doses of histamine by mouth. Perla⁸⁷ found that the injection of sterile solution of sodium chloride intraperitoneally into rats a few hours before an intraperitoneal dose of histamine enabled the animals to tolerate twice the normal lethal amounts.

83 Kellaway, C. H. Bancroft Memorial Lecture. Cellular Response to Injury, *M. J. Australia* **2**: 447, 1938.

84 Abramson, H. A., and Ochs, I. Skin Reactions. VI. A Simple Micro-method for the Assay of Histamine in Mammalian Blood, *J. Lab. & Clin. Med.* **24**: 398, 1939.

85 Farmer, L. Nonspecific "Desensitization" Through Histamine, *J. Immunol.* **36**: 37, 1939.

86 Farmer, L. Experiments on Histamine-Refractoriness. II. Nonspecific "Desensitization" Through Oral Application of Histamine, *J. Immunol.* **37**: 321, 1939.

87 Perla, D. Effect of an Excess of Salt on Resistance to Histamine in Rats, *Proc. Soc. Exper. Biol. & Med.* **41**: 234, 1939.

As mentioned in the section on "Serum Disease," histaminase was found by Foshay and Hagebusch⁸⁸ to be useful in treatment of this condition. In 1930, Best and McHenry⁸⁸ showed that simple saline extracts of various animal organs when used fresh and untreated had the property of destroying the histamine in a solution to which they were added. Thus, an extract of 20 mg of moist kidney could destroy 40 mg of histamine in seventy-two hours. They found that almost every tissue contains an enzyme called histaminase. This year, Rose and Browne⁸⁹ have studied the question of what happens to histamine when it is injected intravenously. In rats, they injected histamine intravenously in amounts equivalent to 0.16 mg per gram of body weight, and then killed the animals at intervals and studied their tissues. In other experiments they had shown that the organs were not capable of destroying histamine, but now they find that the content falls off sharply within thirty to sixty minutes after the injection. This is true of all the organs, with one important exception. The kidney takes up histamine much faster than other organs, the content in fifteen minutes being 480 micrograms, as compared with 79 micrograms for the liver and 64 micrograms for the lung. The authors believe that the increased amount of histamine in the blood represents merely the transport of all the histamine to the kidney, from which it can later be redistributed or disposed of. The point is that histaminase does not represent the only method by which histamine is eliminated. One wonders whether Perla's findings just mentioned may not depend on increased circulation following the injection of solution of sodium chloride, in the same sentence one can point to the good effect of the intravenous use of a solution of sodium chloride on asthma as possibly having a similar basis. There is much to be learned about histamine and so-called histaminase.

TREATMENT OF ASTHMA

The treatment of asthma in the ordinary case is to be conducted on a purely allergic basis, and it is not surprising to have Curschmann,⁹⁰ in Germany, and Salen, Hulting and Nordenfors,⁹¹ in Sweden, report excellent results from the use of an allergen-free environment. Unfor-

88 Best, C. H., and McHenry, E. A. The Inactivation of Histamine, *J Physiol* **70** 349, 1930.

89 Rose, B., and Browne, J. S. L. The Distribution and Rate of Disappearance of Intravenously Injected Histamine in the Rat, *Am J Physiol* **124** 412, 1938.

90 Curschmann, H. Aussichten der Asthmabehandlung im "allergenfreien Milieu," *Fortschr d Therap* **14** 561, 1938.

91 Salen, E. B., Hulting, C., and Nordenfors, B. Bericht uber die Tatigkeit am Heim fur asthmakranke Schulkinder in Stockholm, *Acta med Scandinav* 1935, supp 89, p 85.

tunately, however, in the group of cases of intrinsic asthma management is not so easy. Last year, Keeney⁹² published a preliminary report on the use of epinephrine base in oil—"slow epinephrine" as he called it. Now comes the complete report in a paper by Keeney, Pierce and Gay⁹³. Many patients have been relieved for periods up to sixteen hours by the injection of 0.5 to 1.5 cc. In the symptomatic treatment of hay fever, Keeney⁹⁴ finds epinephrine in oil effective. Murphy and Jones⁹⁵ have also used the preparation, which they say is "of value". Spain, Strauss and Fuchs⁹⁶ have suggested another method by which the absorption of epinephrine can be delayed. They recommend that epinephrine be mixed with a 1:500 dilution of gelatin, which, being a non-toxic, nonantigenic substance, is harmless to the patient and, like peanut oil, is absorbed slowly. Brown⁹⁷ has a paper on theophylline with ethylene diamine, a drug which I agree is useful in treatment of patients with severe asthma who have become refractory to epinephrine. Magnesium sulfate is suggested by Haury,⁹⁸ who through experiments on isolated lungs of guinea pigs found that the drug produces bronchodilatation of from 20 to 45 per cent. Farmer⁹⁹ suggests ethyl carbamate, which he has given by mouth to 30 patients with asthma, in doses of 2 to 4 Gm per day. The attacks were alleviated in 14 of 30 cases. Balyeat¹⁰⁰ does well to warn against the use of morphine in treatment of asthma, which I also find in most cases to do more harm than good. Not only does morphine abolish the cough reflex and depress the respiratory center, as Balyeat claims, but patients may be actually sensitive to morphine, as I have found in several cases.

92 Keeney, E. L. A Slowly Absorbed Epinephrine Preparation, *Bull. Johns Hopkins Hosp.* **62**:227, 1938.

93 Keeney, E. L., Pierce, J. A., and Gay, L. N. Epinephrine in Oil. A New, Slowly Absorbed Epinephrine Preparation, *Arch. Int. Med.* **63**:119 (Jan.) 1939.

94 Keeney, E. L. Epinephrine in Oil. Its Effect in the Symptomatic Treatment of Hay Fever, *J. Allergy* **10**:590, 1939.

95 Murphy, J. A., and Jones, C. A. Slow Epinephrine in the Treatment of Chronic Asthma, *J. Allergy* **10**:215, 1939.

96 Spain, W. C., Strauss, B. A., and Fuchs, A. M. A Slowly Absorbed Gelatin-Epinephrine Mixture, *J. Allergy* **10**:209, 1939.

97 Brown, G. T. Aminophyllin in Asthma, *J. Allergy* **10**:64, 1938.

98 Haury, V. G. The Broncho-Dilator Action of Magnesium and Its Antagonistic Action (Dilator-Action) Against Pilocarpine, Histamine and Barium Chloride, *J. Pharmacol. & Exper. Therap.* **65**:58, 1938.

99 Farmer, L. The Use of Urethane in Symptomatic Treatment of Bronchial Asthma, *J. Lab. & Clin. Med.* **24**:453, 1939.

100 Balyeat, R. M. Morphine. Dangerous Drug in Chronic Asthma. *New Orleans M. & S. J.* **91**:556, 1939.

Helium is still used Barach¹⁰¹ has treated a large series of patients, with good results Now, Maytum¹⁰² and Metz, Wearner and Evans¹⁰³ agree that inhalations of mixtures of helium and oxygen are useful in cases of status asthmaticus chiefly to restore the effectiveness of epinephrine More recently, however, Barach¹⁰⁴ has written about oxygen, claiming that the inhalation of pure, 100 per cent oxygen for short periods has been of great benefit to certain patients with chronic emphysema The same subject is discussed by Boothby, Mayo and Lovelace,¹⁰⁵ who emphasize the virtues of oxygen in treatment of asthma and other conditions

Epinephrine is always of great practical value However, it is well to note that there are reports of 2 cases in which serious trouble followed its use Keeney¹⁰⁶ has described a man of 33, sensitive to ragweed, who had mild asthma in late August and was treated with a 1:100 dilution of epinephrine hydrochloride as a spray Later, however, he was given a dose of epinephrine hydrochloride (0.5 cc of the 1:1,000 solution) subcutaneously and immediately headache and coma developed, which were later found to be due to a large lesion in the left hemisphere involving the visual pathways and causing complete right hemiplegia Gormsen,¹⁰⁷ in Sweden, described the case of a man of 42 with severe asthma who also was treated with the epinephrine spray Inadvertently, he filled his hypodermic syringe not with the 1:1,000 but with the 1:100 solution of epinephrine, and in a few minutes after the injection he died Acute epinephrine intoxication has been described before, and Gormsen found 28 cases in the literature The minimum lethal dose for subcutaneous injection seems to be about 10 mg of epinephrine Meantime, Galgiani, Proescher, Dock and Tainter¹⁰⁸ found that when the membranes of rabbits and cats were sprayed with epinephrine each

101 Barach, A. L. The Use of Helium in the Treatment of Asthma and Obstructive Lesions in Larynx and Trachea, *Ann Int Med* **9** 739, 1935

102 Maytum, C. K. Helium-Oxygen Mixtures in Status Asthmaticus, *J Allergy* **10** 264, 1939

103 Metz, C. W., Wearner, A. A., and Evans, A. E. Therapeutic Use of Helium, *South M J* **32** 34, 1939

104 Barach, A. L. Physiological Methods in the Diagnosis and Treatment of Asthma and Emphysema, *Ann Int Med* **12** 454, 1938

105 Boothby, W. M., Mayo, C. W., and Lovelace, W. R. One Hundred Per Cent Oxygen, *J A M A* **113** 477 (Aug 5) 1939

106 Keeney, E. L. Hemiplegia Following Injection of Epinephrine Hydrochloride, *J A M A* **112** 2131 (May 27) 1939

107 Gormsen, H. A Case of Fatal Epinephrine Intoxication, *Ugeskr f læger* **101** 242, 1939

108 Galgiani, J. V., Proescher, F., Dock, W., and Tainter, M. L. Local and Systemic Effects from Inhalation of Strong Solutions of Epinephrine, *J A M A* **112** 1929 (May 13) 1939

day for three months, the trachea showed loss of cilia and desquamation of the epithelium

A year ago potassium chloride was suggested by Rusk and Kenamore¹⁰⁹ as a drug useful in treatment of urticaria. Since then, Rusk, Weichselbaum and Somogyi¹¹⁰ have studied the concentration of potassium in the blood serum in various allergic states and have found it high. Whereas the average normal content is 19.5 mg per hundred cubic centimeters, in urticaria it is 23.4 mg and in asthma 23.6 mg, and during acute asthma it is 24.4 mg. The blood is merely the medium of transport. The authors' theory is that in allergy the potassium moves from the cells to the blood and that the good effects of insulin and of dextrose in cases of urticaria and of asthma depend on driving potassium back into the cells. By providing an excess of potassium in the diet, the cells can regain their normal potassium content. Meantime, Bloom¹¹¹ claims to have produced striking improvement in 29 patients with hay fever by giving them 25 grains (less than 2 Gm) of potassium chloride per day by mouth. On the other hand, Cohen¹¹² treated 8 patients with chronic urticaria with the diet and the doses of potassium chloride recommended by Rusk and Kenamore, but in no case was improvement shown.

Cyclopropane anesthesia has been used in cases of severe intractable asthma by Meyer and Schotz,¹¹³ who claim dramatic results in 1 case and describe two advantages: first, that the drug works rapidly, and, second, that the anesthetic mixture contains a high concentration of oxygen.

Roentgen treatment has been revived by Maytum and Leddy,¹¹⁴ who have applied it to 161 patients. Marked relief was obtained in only 24 per cent of the patients treated with roentgen rays alone. Others did well, but they had other treatment at the same time.

109 Rusk, H. A., and Kenamore, B. D. Urticaria. A New Therapeutic Approach, *Ann Int Med* **11** 1838, 1938.

110 Rusk, H. A., Weichselbaum, T. E., and Somogyi, M. Changes in Serum Potassium in Certain Allergic States, *J A M A* **112** 2395 (June 10) 1939.

111 Bloom, B. The Use of Potassium Salts in Hay Fever. Preliminary Report, *J A M A* **111** 2281 (Dec 17) 1938.

112 Cohen, A. E. The Treatment of Chronic Urticaria with a High Protein, Low Sodium, Acid-Ash Diet, with Added Potassium Chloride, Case Reports, *J Allergy* **10** 61, 1938.

113 Meyer, N. E., and Schotz, S. The Relief of Severe Intractable Bronchial Asthma with Cyclopropane Anesthesia. Report of Case, *J Allergy* **10** 239, 1939.

114 Maytum, C. K., and Leddy, E. T. Roentgen Treatment of Asthma, *J Allergy* **10** 135, 1939.

Operations on the sympathetic nerves have been described in previous reviews, and now it is interesting to have Leriche and Fontaine ¹¹⁵ report on the late results of stellectomy. They have followed 14 patients, all of them for at least two years and many for a much longer time, and have found that unilateral stellectomy performed on 7 patients resulted in virtual cures in 2 cases, 1 of the patients having been well for thirteen years. Bilateral stellectomy was performed on 7 patients, and 4 of them appear to be "cured."

DRUG ALLERGY

Drug allergy deserves increasing attention chiefly because of the advances in chemistry which have resulted in the exposure of an ever increasing number of persons to an ever larger number of new chemical substances, some of which are found in the large chemical industries while others appear in paints and varnishes, in cleaning fluids and solvents, in fuels, in solutions for photography, in cosmetics and, most important of course, in the host of new drugs or isomers of old drugs which have been recommended as improved remedies for all manner of human ills. Osborne and Jordon ¹¹⁶ say that almost any chemical will produce sensitization, and it therefore becomes important to do everything possible to prevent its development—for example, by the control of industrial dusts and by the better selection of persons to work in contact with them, through exclusion of those with allergic tendencies. Downing ¹¹⁷ has reviewed 2,000 cases of cutaneous eruptions occurring among industrial workers during the past six years. Schwartz ¹¹⁸ states that 1 per cent of the industrial workers in this country are affected each year, persons with oily skins being the most liable. The causative factors are widely distributed but are most important in the metal industry, with domestic and food industries following, in that order. The list of substances to which sensitiveness has been observed is remarkable, as may be seen in the presentation of Rostenberg and Sulzberger, ¹¹⁹ whose list of substances used in patch

115 Leriche, R., and Fontaine, R. Les résultats éloignés au traitement chirurgical de l'asthme bronchique par la stellectomie, *Strasbourg med* **98** 475, 1938

116 Osborne, E. D., and Jordon, J. W. The Practical Aspect of the Prevention of Industrial Dermatoses, *J. A. M. A.* **111** 1533 (Oct 22) 1938

117 Downing, J. G. Cutaneous Eruptions Among Industrial Workers. Review of Two Thousand Claims for Compensation, *Arch. Dermat. & Syph.* **39** 12 (Jan) 1939

118 Schwartz, L. The Incidence of Occupational Dermatoses and Their Causes in the Basic Industries, *J. A. M. A.* **111** 1523 (Oct 22) 1938

119 Rostenberg, A., Jr., and Sulzberger, M. B. A List of Substances for Patch-Testing, and the Concentrations to Be Employed, *J. Invest. Dermat.* **2** 93, 1939

tests covers twenty pages of small type. The recent literature contains additional references to a variety of industrial substances which have been responsible for the dermatitis observed in a number of cases. Any list of these would be out of date by the time it is printed, and so will not be given here. However, several references are interesting. Burckhardt¹²⁰ describes bricklayers' dermatitis in 80 patients who reacted to patch tests and were sensitive to the calcium hydroxide in the lime. Others reacted to the tricalcium aluminate in the cement. Bakers' dermatitis has been studied by Zundel and Jentsch,¹²¹ who found reactions to various persulfates, spice oils and turpentine among the 450 patients studied. It is curious that wheat sensitiveness was not mentioned.

Sulfanilamide has resulted in allergic manifestations, as expected. Tedder¹²² reports three types of toxic manifestations, one of which depends on true sensitivity to the drug. Hallam¹²³ reports the case of a young man who had taken small doses of sulfapyridine for the treatment of urethritis and then was exposed to an ultraviolet lamp. The photosensitivity resulted in severe inflammation of the skin with edema and vesicles. Gallagher¹²⁴ presents the interesting case of a youth of 18 who was treated with sulfanilamide for a sore throat. Two years later, at the age of 20, he acquired acute urethritis and was again given sulfanilamide, in a new dose of 20 grains (1.3 Gm.). That afternoon, he had malaise, headache and fever, and on the third day was covered with a diffuse rash. His white cell count fell from 17,000 to 9,000. Another interesting case is reported by Rogers¹²⁵. A woman, known to have skin sensitivity to various local anesthetics, was treated with sulfanilamide, whereon each and every site in which local anesthetics had been administered previously flared up with a bright erythematous reaction. Rogers points out that aminobenzene is the base common to sulfanilamide and to many local anesthetics.

Karaya gum is of particular importance because it is found so often not only in cosmetics but in domestic and kitchen materials. Bowen¹²⁶ adds 5 cases of sensitiveness to this substance.

120 Burckhardt, W. Das Maurereczem (Eine experimentelle und klinische Studie zur Ekzemfrage), *Arch f Dermat u Syph* **178** 1, 1938.

121 Zundel, W., and Jentsch, M. Die allergischen Vorgänge beim Backer-ekzem und ihre Deutung, *Arch f Dermat u Syph* **178** 469, 1939.

122 Tedder, J. W. Toxic Manifestations in the Skin Following Sulfanilamide Therapy, *Arch Dermat & Syph* **39** 217 (Feb.) 1939.

123 Hallam, R. Severe Skin and General Reaction Following the Administration of M & B 693 and Exposure to Ultra-Violet Light, *Brit M J* **1** 559 1939.

124 Gallagher, J. R. Sulfanilamide Drug Fever. A Second Attack of Sudden Onset, *New England J Med* **221**.132, 1939.

125 Rogers, E. B. Sensitization Reaction to Sulfanilamide, *J A M A* **111** 2290 (Dec 17) 1938.

126 Bowen, R. Karaya Gum as a Cause of Urticaria, *Arch Dermat & Syph* **39** 506 (March) 1939.

Insulin sensitiveness is of some practical importance because the cases are not rare. Kern and Langner¹²⁷ have studied the mechanism by which the condition develops, pointing out that it occurs more often in nondiabetic than in diabetic persons, for, as is usual in cases of drug allergy, the classic method of producing sensitiveness is to provide for two courses of treatment with an interval between. The treatment of insulin hypersensitiveness does not appear to be difficult. In Corcoran's¹²⁸ patient urticaria developed, but with a series of doses given a few minutes apart, at first intracutaneously, then subcutaneously and finally intravenously, desensitization was accomplished in about fifteen hours. Ulrich, Hooker and Smith¹²⁹ had a similar experience, for repeated desensitization with doses given at intervals of thirty to sixty minutes changed the reaction so that, whereas the first dose of 0.1 cc caused a large wheal 23 by 33 mm in diameter at 10:30 a. m., the thirteenth dose, consisting of twice the quantity, produced no reaction at all at midnight. As a matter of fact, one would suppose that the routine method by which insulin is given in one or two doses each day would be the ideal treatment for any sensitiveness to it.

OTHER ALLERGIC DISEASES OF THE SKIN

Sensitivity to poison ivy has been studied. As Simon and Lotspeich¹³⁰ point out, sensitiveness does not occur in all persons exposed, and so must depend on a predisposing factor. Specific treatment is sometimes helpful from the clinical point of view, but the fact is that cutaneous tests made by a careful technic with serial dilutions of ivy extract showed that the treatment had produced little difference in the strength of the reaction afterward. Zisserman and Birch¹³¹ observed 304 boys at a scout camp who were treated with an ether extract of poison ivy suspended in olive oil. In spite of treatment, 51.6 per cent of the boys had dermatitis. A control group of 241 boys were found from their histories to be susceptible to poison ivy, but were nevertheless left untreated. Of this group dermatitis occurred in 60.6 per cent. The differences between the groups were small.

127 Kern, R. A., and Langner, P. H. Protamine and Allergy. I. Nature of the Local Reactions After Injections of Protamine Zinc Insulin, II. Induction of Sensitivity to Insulin by Injections of Protamine Zinc Insulin, *J. A. M. A.* **113** 198 (July 15) 1939.

128 Corcoran, A. C. Note on the Rapid Desensitization in a Case of Hypersensitiveness to Insulin, *Am. J. M. Sc.* **196** 359, 1938.

129 Ulrich, H., Hooker, S. B., and Smith, H. H. Allergic Reaction to Insulin. Report of a Case, *New England J. Med.* **221** 522, 1939.

130 Simon, F. A., and Lotspeich, E. Observations on Sensitivity to Poison Ivy, *J. Invest. Dermat.* **2** 143, 1939.

131 Zisserman, L., and Birch, L. The Prophylaxis and Treatment of Poison Ivy Dermatitis with an Extract of *Rhus Toxicodendron*, *J. Allergy* **10** 596, 1939.

Meantime, Landsteiner and Chase¹³² have studied the question of how the whole skin becomes sensitive. They repeated Strauss's original experiment, except that this time the isolated islands of skin to be tested were separated by a deep incision involving the muscular layer, and therefore cutting the lymphatics which lie between this muscle and the skin itself. When this was done, the sensitiveness produced on the treated island did not spread beyond it. This and other experiments show that sensitiveness to poison ivy spreads through the lymphatics and not by direct contact between one skin cell and the next.

Atopic dermatitis is that form of so-called eczema which has a typical distribution to the face, neck and cubital and popliteal spaces and which is associated with positive cutaneous reactions and the presence of passive transfer bodies in the blood. Its mechanism appears to be comparable with that of hay fever and asthma, and the condition can be conceived of as "asthma of the skin." The cause of trouble comes not by direct contact but through the blood vessels underneath the skin. In children at least, foods often appear to be the offending substances, and the elimination of eggs, or perhaps milk, has given relief in a number of cases. In view of its blood-borne cause of the condition, it is not surprising that Feinberg,¹³³ as well as Osborne and Walker,¹³⁴ states that dusts can cause atopic dermatitis. Feinberg has studied 14 patients who gave a definite seasonal history of dermatitis and in whom cutaneous tests showed positive reactions to pollens and to fungi. They were benefited greatly by treatment. I, too, have seen such patients and have found that, in addition to pollen, the other dust substances of domestic origin—kapok and cottonseed, as well as the animal danders—are occasional causes of atopic dermatitis.

Fungous dermatitis can give a clinical picture which is almost indistinguishable from that of contact dermatitis and of atopic dermatitis. Moreover, any two, or even all three, of these conditions can coexist in the same patient. The literature on this problem is large, too large to review here, particularly as an excellent analysis has recently been presented by Goodman and Sulzberger.¹³⁵ Two papers seem to be of practical value. Berberian¹³⁶ found that if socks made of silk, wool or

132 Landsteiner, K., and Chase, M. W. Studies on the Sensitization of Animals with Simple Chemical Compounds. VI. Experiments on the Sensitization of Guinea Pigs to Poison Ivy, *J. Exper. Med.* **69** 767, 1939.

133 Feinberg, S. M. Seasonal Atopic Dermatitis. The Role of Inhalant Atopens, *Arch. Dermat. & Syph.* **40** 200 (Aug.) 1939.

134 Osborne, E. D., and Walker, H. L. Contact and Environmental Allergens as a Cause of Eczema in Infants and in Children, *Arch. Dermat. & Syph.* **38**:511 (Oct.) 1938.

135 Goodman, J., and Sulzberger, M. B. Allergy in Dermatology, *J. Allergy* **10** 481, 1939.

136 Berberian, D. A. Dermatophytosis of Feet. Sources and Methods of Prevention of Reinfection, *Arch. Dermat. & Syph.* **38**:367 (Sept.) 1938.

cotton are placed in a flask of water and are incubated, the fungus can be cultivated easily. Inner soles and even leather itself make a good substrate for the growth of the fungus. Ordinary laundering has no effect on it, but exposure to formaldehyde vapor for as short a time as twelve hours is sufficient to kill the organisms in shoes and socks. Cutaneous tests with fungus extracts produce allergic reactions of the delayed inflammatory tuberculin type. Lewis, MacKee and Hopper¹³⁷ declare that positive reactions can always be obtained in the presence of a dermatophytid or of an acute inflammatory lesion of fungous origin. More important, however, is the second statement that a negative reaction rules out a mycotic cause. The difficulty, however, is that the test is specific, and so its result must depend on the genus of the causative organism and, consequently, on the nature of the test material.

At the end of this rapid and sketchy review, in which it is quite impossible to touch any but the "high spots," it is most appropriate to quote a sentence from that remarkable autocrat Dr. Oliver Wendell Holmes, who declared: "Knowledge and timber shouldn't be used till they are seasoned."

263 Beacon Street

¹³⁷ Lewis, G. M., MacKee, G. M., and Hopper, M. E. The Trichophyton Test: Its Value as a Diagnostic Aid, *Arch. Dermat. & Syph.* **38**: 713 (Nov.) 1938.

Obituaries

HARVEY CUSHING, M D

1869-1939

The editorial board of the Archives feels a distinct sense of personal loss in the death of Dr Harvey Cushing. He was a contributor to our journal from time to time,¹ in 1927 with L M Davidoff, in 1932 with M N Fulton, and in 1933 when he submitted for publication "‘Dyspituitarism’ Twenty Years Later," a Harvey Society lecture in which he described his own conception of the clinical aspects of pituitary basophilism. He was one of our meticulous critics, making no bones about his dislike for certain of our peculiarities of spelling, punctuation or syntax. But at the same time he was a staunch friend—the first to congratulate us on work well done, the last to criticize our failings behind our back, and always one of our sincerely interested, inquisitive readers.

Dr Cushing, as every one knows, was a doctor of unusual versatility. He was a distinguished brain surgeon, the most distinguished in the world of his time, founder of a whole school of neurosurgeons whose accomplishments now encircle the globe. He was an imaginative clinical investigator. He was an expert medical bibliophile and historian. He was an eminent teacher. He was a fine writer, and hence was adroit with both the scalpel and the pen, as President Lowell aptly said in awarding him an honorary degree at Harvard. This was no perfunctory compliment suitable to the occasion and meaning little else, for Dr Cushing's nonmedical writings—the "Life of Sir William Osler" (1925), "Consecratio Medici and Other Papers" (1928), and "From a Surgeon's Journal 1915-1918" (1936)—have interested a wide range of readers, have inspired medical students almost as much as did Cushing's skill in the operating room and have stimulated many a doctor to better literary efforts.

Dr Cushing was never conceited or boastful of his reputation as an author. Two years ago he answered a friend, in reply to a request for a copy of his complete bibliography: "You will remember how horrified

1 Cushing, H, and Davidoff, L M. Studies in Acromegaly. IV. The Basal Metabolism, *Arch Int Med* **39**:673-697 (May) 1927. Davidoff, L M, and Cushing, H. Studies in Acromegaly. VI. The Disturbances of Carbohydrate Metabolism, *ibid* **39**:751-779 (June) 1927. Fulton, M N, and Cushing, H. The Specific Dynamic Action of Protein in Patients with Pituitary Disease, *ibid* **50**:649-667 (Nov) 1932. Cushing, H. "Dyspituitarism" Twenty Years Later, with Special Consideration of the Pituitary Adenomas, *ibid* **51**:487-557 (April) 1933.

Osler was, shortly before his end, to receive Miss Minnie Blogg's published list of his bibliography. I have much the same feeling about my own past papers, many of which were ephemeral and written only because I got pushed into contributing something for a medical meeting



HARVEY CUSHING, M D
1869-1939

here and there. As a matter of fact, I think you have all the original papers bound from 1920 to 1933, and of those written before and since that time, the less said the better."

Dr. Cushing took chief pride in being a clinician. He once said with deep feeling, when he suspected that the laboratory side of medicine

was becoming overemphasized, "We have instruments of precision in increasing numbers with which we and our hospital assistants at untold expense make tests and take observations, the vast majority of which are but supplementary to, and as *nothing* compared with, the careful study of the patient by a keen observer using his eyes and ears and fingers and a few simple aids. The practice of medicine is an art and can never approach being a science even though it may adopt and use for its purposes certain instruments originally designed in the process of scientific research."² These words summarized his own philosophy as to how the advancement of medical knowledge could best be obtained, in his own clinical work he steadily maintained this viewpoint and taught it to his assistants.

The copy of Morgan's "Discourse upon the Institution of Medical Schools in America" in his library had come to him directly from his great-grandfather, Dr. David Cushing, through the hands of his grandfather, Dr. Erastus Cushing, his father, Dr. Henry Cushing, and his brother, Dr. Edward Cushing. Dr. Harvey Cushing would ask no higher compliment than to be thought of as one of the medical profession who did his job as best he could, at last achieving an honorable place beside the other medical members of his family in that select company of practitioners whose work makes them forever to be respected.

² Cushing, H. Medicine at the Crossroads, J. A. M. A. **100** 1567-1575 (May 20) 1933.

Book Reviews

Der Magenkrebs By Georg Ernst Konjetzny, M.D., Professor of Surgery of Hansische University, Hamburg, Germany Cloth Price, 26 80 marks Pp 289, with 155 illustrations Stuttgart Ferdinand Enke, 1938

This book will be welcomed by every one interested in the subject of gastric cancer, for it contains the results of Konjetzny's life work. The author is a recognized authority, and in this volume he presents new material and fits it together with older observations to present a complete picture, not only of the development of gastric carcinoma but of present day therapeutics of the most common visceral malignant change. In view of the impossibility of preventing cancer, early diagnosis and radical surgical measures are needed.

There is a certain inherited tendency or organic disposition to carcinoma, but cancer as such is not inherited. Cancer is apparently neither contagious nor infectious. The Cohnheim theory of development from immature embryonal cells has been discarded. Trauma is not significant except as it relates to the results of destruction of the mucosa, as in acid or alkali poisoning, with subsequent regeneration and heteroplasia. Konjetzny accepts the Virchow theory of the role of local disease processes in the development of tumors and devotes a considerable portion of the monograph to the thesis that the chronic inflammatory conditions of great significance as a basis for carcinoma are chronic gastritis with its sequelae and gastric ulcer. Konjetzny has spent thirty years working on the relation between chronic gastritis, benign ulcer and carcinoma. Gastritis is thought by him to be the basis for both ulcer and carcinoma. Gastric carcinoma is always associated with definite chronic atrophic or atrophic-hyperplastic gastritis and never appears in a perfectly normal mucosa. The important process is the regeneration in the mucosa resulting from the chronic inflammation. The transition from gastritis to polyp formation and carcinoma is illustrated in detail. The carcinomatous change is thought to be multicentric, taking place in the cells of a broad area of the mucosa.

It is not possible by clinical methods alone to demonstrate the carcinomatous transformation of a benign ulcer. The histologic evidence is more definite, although difficulties exist there also. The diagnosis must be deduced from a careful analysis of all the evidence, for no single finding is pathognomonic. Carcinoma may arise in the edge of an ulcer or in the neighboring mucosa independent of the ulcer and because of the gastritis. The gastritis associated with ulcer is perhaps somewhat more acute than that associated with carcinoma, but on the whole there is little, if any, difference between the two types.

The histologic types of carcinoma are variable, are not to be correlated with the gross appearances and from a clinical standpoint are not significant. The gross forms are of prognostic importance. The polypoid intraluminal tumors and the ulcerated dishlike well walled-off growths do not usually metastasize as early as those in which the infiltration extends indefinitely out beyond an area of ulceration or those in which there is no ulceration but mere diffuse infiltration.

Treatment should be directed toward early and radical resection in all cases of carcinoma and of such precarcinomatous states as polypoid gastritis. Konjetzny urges a thorough investigation, including fecal and gastric analysis and roentgen and gastroscopic examination, of all patients with digestive symptoms. Exploratory laparotomy as a diagnostic procedure is not justifiable because of the high degree of reliability of the other clinical methods. Small carcinomas often cannot be palpated. Hence, all areas clinically suspicious should be resected. The only contraindication to resection of gastric carcinoma is the presence of proved distant metastases or extensive carcinomatous peritonitis. Undue pessimism is not justi-

fiable even in regard to the younger patients In the Breslau (Germany) Clinic the longest cure (twenty-one years) occurred in a man operated on at the age of 31 Significant palliative effects may be obtained even when Krukenberg tumors are present

The Principles and Practice of Medicine, Designed for the Use of Practitioners and Students of Medicine. Originally written by the late Sir William Osler, Bart, M D, F R T P, F R S, formerly Regius Professor of Medicine, Oxford University, Professor of Medicine, Johns Hopkins University, Professor of the Institute of Medicine, MacGill University, Professor of Clinical Medicine in the University of Pennsylvania Revised by Henry A Christian, M D, L L D, S D, F R C P, Hersey Professor of the Theory and Practice of Physic, Harvard University, Physician in Chief, Peter Bent Brigham Hospital (The ninth, tenth, eleventh and twelfth editions of this book were revised by Thomas McCrae, M D, F R C P, formerly Professor of Medicine of Jefferson Medical College, Philadelphia) Thirteenth edition Price, \$9 Pp 1,450, illustrated New York D Appleton-Century Company, Inc, 1938

From the time of its first appearance in 1892, Osler's "Principles and Practice of Medicine" has been the most valued guide to the practice of medicine in the English language Its use as a reference has been worldwide This prestige has been maintained through subsequent editions prepared under Dr Osler's hand and later under the hand of his student and friend Dr McCrae The new thirteenth edition is prepared by another former pupil and friend, Dr Henry A Christian, and fully maintains the standard set by the former editions It is inevitable that extensive changes should be made The text has been rewritten in part, to include the most recent advances in medical knowledge and practice Some portions have been deleted, and extensive changes made which Dr Osler would have been the first to make had he been preparing the edition A student of the earlier text may feel a little strange to open at pneumonia instead of typhoid and not to find other subjects in their accustomed places But the book has been rearranged and rewritten with a sympathetic understanding of the broad aims of Dr Osler's first text and, in spite of changes, adheres to the Osler tradition The volume offers the advantage of a uniformity of point of view and teaching which only a text written by one man can offer, and its value is further enhanced by the clinical experiences and broad scholarship of Dr Christian

A Guide to Human Parasitology for Medical Practitioners By D B Blacklock, M D (Edinburgh), D P H (London), D T M (Liverpool), Professor of Tropical Hygiene, Liverpool School of Tropical Medicine, University of Liverpool, formerly Professor of Parasitology, and Director of the Sir Alfred Lewis Jones Laboratory, Freetown, Sierra Leone, West Africa, and T Southwell, D Sc, Ph D, A R C Sc, F Z S, F R S E, Walter Myers Lecturer in Parasitology, School of Tropical Medicine, University of Liverpool, formerly Director of Fisheries to the Governments of Bengal and Bihar and Orissa, Scientific Advisor and Inspector of Pearl Banks to the Ceylon Company of Pearl Fishers, and Honorary Assistant, Zoological Survey of India Third edition Price, \$4 Two colored plates and 122 illustrations Baltimore William Wood & Company, 1938

This volume has been prepared for ready reference on the subject of human parasitology by the practicing physician This purpose it fulfils admirably As is inevitable when so broad a subject is to be presented in one small volume, a rather limited consideration must be given to each subject A few minor omissions might have been made to allow more space for the subject in hand

It would seem hardly necessary in a book prepared for physicians to waste space on a chapter devoted to the care and use of the microscope or to include even an abbreviated consideration of blood examination Also the group of spiro-

chaetacia should have been left to the bacteriologist. This space could have been used advantageously in expanding a valuable text on the subject of animal parasites.

A bibliography which would include not only the larger texts but detailed references to the special subject for students would be an advantage. The book as it is is clear and comprehensive and is of value to the practitioner for whom it is designed.

Fundamentals of Experimental Pharmacology By Torald Sollmann and Paul J. Hanzlik. Second edition. Price, \$4.25. Pp. 307, with illustrations. San Francisco: J. W. Stacey, Inc., 1939.

The second edition of this well known manual does not differ in form or general arrangement from the first. Structural formulas for certain of the alkaloids have been changed to agree with present day views. Experiments with recently introduced drugs—evipal, pentobarbital, avertin with amylene hydrate and sulfanilamide—have been added. One of the most valuable features of both the first edition and the older manual of the senior author which preceded it is the table of doses suitable for laboratory animals. The new edition extends the list considerably and contains a tremendous amount of material that is elsewhere scattered through an extensive literature. Many of the doses have been confirmed in the laboratories of the authors. Few errors have been noted by this reviewer, the most serious one being the statement that digitalis is said to be assayed against ouabain in the eleventh revision of the United States Pharmacopeia. Ouabain has been retained as a standard for strophanthin but not for digitalis. Probably no active laboratories of pharmacology in this country have been without the predecessor of this manual, and it is likely that the present edition will maintain the status of the first.

Affections non ulcéreuses du duodenum By I. Pavel and A. Paunesco-Podeano. Paper. Price, 50 francs. Pp. 204, with 57 illustrations. Paris: Masson & Cie, 1938.

This publication of Pavel and Paunesco-Podeano on nonulcerative diseases of the duodenum is unique. The authors include discussions of normal and abnormal physiology of the duodenum along with fairly complete descriptions of non-ulcerative duodenal clinical syndromes and their treatment. Among the conditions presented are pseudoulcerative duodenitis, hemorrhagic duodenitis, chronic duodenitis with icterus, phlegmonous duodenitis, diverticulation of the duodenum, duodenal stasis (mechanical and functional) and tumors and congenital malformations of the duodenum. Each condition is presented in routine textbook fashion, with a tendency to emphasis on the clinical aspects. Each chapter is concluded with an extensive and predominantly European bibliography on its subject.

The monograph deserves a high place among those on various phases of gastroenterology. It is a good collection of practical data on nonulcerative duodenal disease. Every one interested in internal medicine, and especially in gastroenterology, will find many helpful clinical ideas.

Marihuana, America's New Drug Problem: A Sociologic Question with Its Basic Explanation Dependent on Biologic and Medical Principles By Robert P. Walton, Professor of Pharmacology, School of Medicine, University of Mississippi, with a foreword by E. M. K. Geiling, Professor of Pharmacology, University of Chicago, and a chapter by Frank R. Gomila, Commissioner of Public Safety, New Orleans, and M. C. Gomila Lambou, Assistant City Chemist. Cloth. Price \$3. Pp. 223, with 17 figures and illustrations. Philadelphia: J. B. Lippincott Company, 1938.

Knowledge concerning the drug problem presented by marihuana has come to most physicians through the somewhat sensational news stories in the supplements

of the Sunday newspapers Dr Walton's exhaustive monograph concerning the narcotic principles of the drug is extremely timely. The book is factual but interestingly written. It covers the historical, botanic, pharmacologic, sociologic, legal and public health aspects of the use, or more specifically the misuse, of marihuana. There is a valuable chapter on nomenclature, which gives a complete glossary. The bibliography contains 419 references. The book should prove an invaluable reference for sociologists, public health officers and physicians.

The Genuine Works of Hippocrates. Translated from the Greek by Francis Adams. Price, \$3.00. Pp 384, with 8 plates. Baltimore. The Williams & Wilkins Co., 1939.

The reviewer is unable to discuss critically the merit of various Hippocratic texts and translations, but from the standpoint of the bibliophile one can only be pleased with this handsome edition of the Adams version. The book is well printed on fine paper and in general is obviously a superior piece of book making. The publishers are to be congratulated.

Notices

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Requests have been received for a twenty year index of the ARCHIVES OF INTERNAL MEDICINE. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed \$5 a copy. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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HYPERTROPHY AND HYPERPLASIA OF ISLANDS OF LANGERHANS IN INFANTS BORN OF DIABETIC MOTHERS

ELSON B. HELWIG, M.D.

BOSTON

Owing to the inadequate therapy available for diabetic patients even for some time after insulin became available, the fertility of diabetic women was low and pregnancy a rarity. When better control of the diabetic state made it possible for pregnancy to occur, it was disconcerting to observe that some of the infants were born dead and that others died soon after birth. Autopsies on these infants showed no consistent pathologic change.

The chemical and postmortem observations suggested a low blood sugar level, and to explain this Dubreuil and Andérodias¹ and others²

From the Pathological Laboratory of the New England Deaconess Hospital

1 Dubreuil, G., and Andérodias. Ilots de Langerhans géants chez un nouveau-né, issue de mère glycosurique, *Compt rend Soc de biol* **83** 1490, 1920

2 (a) Wiener, H. J. Diabetes Mellitus in Pregnancy, *Am J Obst & Gynec* **7** 710, 1924. (b) Gray, S. H., and Feemster, L. C. Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, *Arch Path* **1** 348 (March) 1926. (c) Feldmann, I. Diabetes intrauterina, *Centralbl f allg Path u path Anat* **42**:435, 1928. (d) Schretter, G., and Nevinny, H. Zur Histopathologie der Zuckerkrankheit bei Neugeborenen und Säuglingen, *Arch f Gynak* **143** 465, 1930. (e) Nothmann, M., and Hermstein, A. Diabetes und Gravidität, *ibid* **150**:287, 1932. (f) Bowen, B. O., and Heilbrun, N. Pregnancy and Diabetes, with a Report of Five Cases and a Review of the Literature, *Am J M Sc* **183** 803, 1932. (g) Jacobsen, N. S. Insulin Coma in Pregnant Diabetics, *Ugesk f læger* **96**:347, 1934. (h) Ehrlich, W. Ueber angeborene Hypoglykämie, *Klin Wchnschr* **13** 584, 1934. (i) Gordon, W. H. Fetal Hypoglycemia Due to Hyperinsulinism, *J Michigan M Soc* **34** 167, 1935. (j) Gordon, W. H. Compensatory Hypertrophy and Hyperplasia of Islands of Langerhans in Utero. Congenital Hypoglycemia Due to Hyperinsulinism, *Ohio State M J* **32** 540, 1936. (k) Randall, L. M., and Rynearson, E. H. Delivery and Care of the Newborn Infant of the Diabetic Mother, *J A M A* **107**:919 (Sept 19) 1936. (l) Hartman, A. F., and Jaudon, J. C. Hypoglycemia, *J Pediat* **11** 1, 1937. (m) Nakamura, N. Untersuchungen über das Pankreas bei Föten, Neugeborenen, Kindern, und im Pubertätsalter, *Virchows Arch f path Anat* **253** 286, 1924. (n) Angyal, F. Hypertrophie der Langerhansschen Inseln

(Footnote continued on next page)

have suggested transient fetal hyperinsulinism accompanying hyperplasia of the islands of Langerhans

To determine whether an adequate structural basis existed for the assumed hyperinsulinism, the pancreatic islands in 9 infants of diabetic mothers and 9 infants of normal mothers were studied

From a block of tissue previously selected at random from each pancreas, approximately 90 serial sections were cut and stained with phloxine and methylene blue (methylthionine chloride U S P) By observing the islands in the consecutive sections, the maximal dimensions of each island were determined in two diameters at a standard magnification by means of a calibrated eye piece micrometer Only those islands which increased in size when examined in serial sections were included in the determination of the maximal diameters, islands not sectioned through the point of maximal diameters thus being excluded

Because of the appreciable variation in the maximal diameters of the various islands, an average of them would not fairly represent the large, irregular islands or the small islands Although their shape is varied, ranging as they do from spheres through a wide variety of figures, a fair number of the islands may be reduced in sectional outline to a rough parallelogram I have consequently adopted the product of the diameters of each island as representing its maximal cross-sectional area Obviously, this arbitrary choice has introduced a certain element of error, but it is no more than would have been introduced by using the diameters severally, or by assuming a different shape to be the standard Since the pancreases of both the control series and the infants of diabetic mothers were measured and calculated in the same way, I feel that the results of the two series are fairly comparable

CONTROL SERIES

CASE 1—A tertipara aged 24 delivered spontaneously a boy of seven months' gestation, weighing 4 pounds 4 ounces (1,928 Gm) The baby breathed with difficulty and died twenty-nine hours after birth There was a history of other premature births of infants with the same respiratory difficulty

At autopsy the right lateral ventricle of the brain contained blood-tinged fluid, and the choroid plexus was enlarged, dark red, and surrounded by a blood clot

in der Frucht einer zuckerkranken Schwangeren, Centralbl f allg Path u path Anat **66** 209, 1936 (o) Bauer, J T, and Royster, H A, Jr Hypoglycemia, Hypertrophy and Hyperplasia of Islands of Langerhans in the Newborn Infant Following Maternal Diabetes Report of a Case Associated with Tetany, and Review of the Literature, Bull Ayer Clin Lab, Pennsylvania Hosp **3** 109, 1937 (p) Rascoff, H, Beilly, J S, and Jacobi, M Hyperglycemia of Newborn Associated with Hypertrophy and Hyperplasia of Islands of Langerhans, Am J Dis Child **55** 330 (Feb) 1938 (q) Heiberg, K A Das Inselgewebe bei einem neugeborenen Kinde einer zuckerkranken Mutter, Virchows Arch f path Anat **287** 629, 1933

The lungs showed partial atelectasis. The pancreas appeared normal. Microscopically, there was a moderate number of islands varying in size from a few cells to those with diameters of 239 by 231 microns. There were a few minute foci of hemopoiesis.

CASE 2—A primipara aged 28 was delivered by cesarean section supposedly one week after term, because of vaginal bleeding and a decreased heart rate of the infant. The uterus was filled with blood, and the umbilical cord, only 25 cm long, was torn near the umbilicus. The boy weighed 5 pounds $\frac{1}{2}$ ounce (2,284 Gm) and breathed well, but died fifteen minutes after delivery.

At autopsy the pancreas appeared normal. Microscopically there was a moderate number of islands, which varied in size from masses containing a few cells to some with diameters of 169 by 154 microns. The islands appeared normal. No hemopoiesis was noted.

CASE 3—A primipara aged 30 had a low forceps delivery, somewhat prematurely, of a boy weighing 6 pounds 8 ounces (2,948 Gm). Respiration was difficult, and the baby died one and one-half hours after birth.

At autopsy the pancreas appeared grossly normal. Microscopically, there was a moderate number of islands, which varied in size from masses containing a few cells to some with diameters of 231 by 308 microns. There were a few minute foci of hemopoiesis.

CASE 4—A primipara aged 27 delivered without incident a well developed full term boy, weighing 8 pounds $6\frac{1}{2}$ ounces (3,814 Gm). Respirations were and died sixty hours after birth.

Autopsy showed cor batriatum triloculare. The pancreas was moderately firm, gray and elastic. Microscopically, there was a moderate number of islands, which varied in size from masses containing a few cells to some with diameters of 292 by 185 microns. There were a few very small foci of hemopoiesis.

CASE 5—A primipara aged 41 after an unsuccessful trial labor delivered by cesarean section a full term, well developed girl. Although the heart sounds were good, the baby failed to breathe.

At autopsy the lungs were atelectatic and the pancreas grossly normal. Microscopically, there was a moderate number of generally small islands, which varied in size from masses containing a few cells to some with diameters of 308 by 192 microns. No foci of hemopoiesis were noted.

CASE 6—A tertipara aged 31, after four hours of easy labor delivered a full term boy, weighing 8 pounds $6\frac{1}{2}$ ounces (3,814 Gm). Respirations were shallow and the baby died four hours after delivery.

Autopsy disclosed tears in the tentorium cerebelli, hemorrhage into the subarachnoid spaces and petechiae in the brain. The pancreas appeared normal. Microscopically, there was a moderate number of islands, which varied in size from masses containing a few cells to some with diameters of 262 by 208 microns. There were rare minute foci of hemopoiesis.

CASE 7—A secundipara aged 29 was delivered by breech extraction. The infant, a boy weighing 8 pounds 8 ounces (3,856 Gm), died immediately after birth.

At autopsy the lungs were atelectatic. The pancreas appeared normal. Microscopically, there was a moderate number of islands, which varied in size from

masses containing a few cells to some with diameters of 262 by 192 microns. The island cells appeared normal, except for a few with a very slightly increased amount of cytoplasm. There were scattered foci of hemopoiesis.

CASE 8—A *tertipara* aged 30 delivered normally a boy weighing 8 pounds 8 ounces (3,856 Gm). The baby did not breathe well, had slight jaundice and died twenty-one hours after birth.

At autopsy the pancreas was normal. Microscopically, there was a moderate number of islands, which varied in size from masses containing a few cells to some with diameters of 262 by 192 microns. The islands generally appeared normal, but in a few the cells were slightly larger than average, with an occasional enlarged nucleus. The interlobular stroma contained a few minute foci of hematopoiesis.

CASE 9—A *tertipara* aged 40 had a low forceps delivery. One week before parturition she had become slightly toxic. The boy, weighing 8 pounds 15 ounces (4,058 Gm), was slow to breathe. Later breathing was rapid, with poor color and twitching. The baby died forty-two hours after delivery.

At autopsy the pancreas appeared normal. Microscopically, the islands were moderately numerous and varied in size from masses containing a few cells to some with diameters of 654 by 447 microns. Many of the islands, particularly the smaller ones, appeared normal. In the larger islands the cells were larger than normal, with an increased amount of cytoplasm which stained highly acidophilic. Generally the nuclei were slightly larger than the average, and occasionally they were much larger. A few islands showed both types of cells. Some of the islands exhibited an increase of supporting stroma. Rarely, eosinophilic myelocytes, some of which were mature, were noted in the islands. There were a few scattered minute foci of hemopoiesis in the stroma.

DIABETIC SERIES

CASE 1—A *primipara* aged 26 was first noted to have diabetes in March 1932. The last catamenia was probably in September 1936. She received unmodified and protamine insulin. Thirteen samples of blood, taken at intervals from Dec 5, 1936 to Feb 26, 1937, on four occasions contained between 200 and 250 mg of dextrose per hundred cubic centimeters, once 300 mg and once 330 mg per hundred cubic centimeters. The remainder of the values were below 200 mg per hundred cubic centimeters. On Feb 27, 1937, she was delivered spontaneously of a boy weighing 3 pounds $\frac{1}{2}$ ounce (1,314 Gm). The baby died shortly after birth. The placenta showed localized infarction, and the umbilical cord showed foci of acute inflammation. The autopsy, performed eight and one-half hours after death, disclosed a normally developed but immature infant, weighing 1,380 Gm and measuring 15 cm in length (crown-rump). The lungs were atelectatic, otherwise all organs appeared normal. The pancreas weighed 0.8 Gm. Microscopically, the islands were not numerous, were generally small and varied in size from masses containing a few cells to some with diameters of 308 by 231 microns. The island cells and the nuclei were of average size. No mitotic figures were noted. The stroma was relatively prominent and contained scattered hemopoietic cells. Eosinophilic myelocytes were rare.

CASE 2—An *octipara* aged 34 had had diabetes since June 1930. The last catamenia was probably in October 1934. She received insulin. She was in her sixth month of pregnancy when she was admitted to the hospital, Jan 8, 1935, in

TABLE 1—Data on Infants of Nondiabetic Mothers

Infants of Nondiabetic Mothers	Number of Islands Measured	Mean Area of Islands in Square Microns	Standard Deviation of Mean Area of Islands	Diameters of Islands in Microns			Maximum Diameter of Any One Island	Weight of Baby	Duration of Pregnancy	Sex	Duration of Life of Baby
				Largest	Median	Smallest					
1	147	17,688	9,329	239 by 231	131 by 115	85 by 77	254	4 lb 4 oz	7 mo	Male	29 hr
2	186	10,139	3,793	169 by 154	100 by 85	69 by 69	169	5 lb ½ oz	1 week beyond term*	Male	15 min
3	115	23,136	11,211	231 by 208	162 by 131	100 by 85	308	6 lb 8 oz	Full term	Male	1½ hr
4	155	15,938	8,466	292 by 185	123 by 108	77 by 69	292	6 lb 15 oz	Full term	Male	60 hr
5	204	11,554	6,701	308 by 192	100 by 92	92 by 62	308	Well developed	Full term	Female	1½ hr
6	167	15,381	5,660	262 by 208	123 by 100	85 by 69	262	8 lb 6½ oz	Full term	Male	4 hr
7	144	16,554	9,411	262 by 192	139 by 100	77 by 77	277	8 lb 8 oz	Full term	Male	4 hr
8	145	16,237	7,893	262 by 192	139 by 100	77 by 77	262	8 lb 8 oz	Full term	Male	Died immedi- ately after birth
9	122	35,715	41,916	654 by 447	162 by 139	85 by 77	654	8 lb 15 oz	Full term	Female	21 hr
* Estimated									Full term	Male	42 hr

acidosis The carbon dioxide-combining power of the plasma on two occasions was 16 and 10 volumes per cent, and the blood contained 260 and 250 mg of dextrose per hundred cubic centimeters She was given a clysis of 1,500 cc of 5 per cent dextrose in physiologic solution of sodium chloride

Three hours before the mother miscarried, on the day following her admission, the carbon dioxide-combining power was 17 volumes per cent, and the blood contained 320 mg of dextrose per hundred cubic centimeters The boy lived half an hour The mother contracted pneumonia, which was terminated by crisis on the sixth day

Autopsy, performed one-half hour after death, showed an immature infant measuring 36 cm from crown to heel The heart blood contained 220 mg of dextrose per hundred cubic centimeters The organs appeared normal The pancreas measured 2.5 cm in length and 0.4 cm in thickness Microscopically, there were numerous islands, which varied in size from masses containing a few cells up to some with diameters of 439 by 262 microns The island cells were slightly larger than normal, and the nuclei were occasionally considerably enlarged Rarely, mitotic figures were noted The stroma surrounding many of the islands was increased and moderately infiltrated with myelocytes, mostly eosinophilic and mature The stroma elsewhere contained scattered hemopoietic cells The acinar cells were less well developed than the island cells, but otherwise they appeared normal The ducts and blood vessels appeared normal

CASE 3—A primipara aged 25 had had diabetes since March 1934 Her last catamenia was on Oct 9, 1936 In Jan 1937 she was transferred from a regimen of unmodified insulin to one of protamine insulin During April she evidenced a low renal threshold, with as much as 92 Gm of sugar in the urine in one day Tests were made on twenty-four samples of blood, taken at intervals from January to May On one occasion the dextrose content reached 200 mg and on another 330 mg per hundred cubic centimeters, in the remainder of the tests the values were 190 mg or less On May 30, 1937, the mother delivered a boy by the natural route The mother's blood at delivery contained 190 mg of dextrose per hundred cubic centimeters The cord blood of the infant contained 160 mg The carbon dioxide-combining power of the plasma was slightly reduced, and the non-protein nitrogen content of the blood was normal The baby cried feebly, one and one-half hours after birth, the content of dextrose in the infant's blood was 110 mg, and four and one-half hours after birth, 60 mg, per hundred cubic centimeters, the breathing was shallow, and cyanosis developed The baby died six and three-fourths hours after birth

Autopsy, performed five hours after death, showed a well developed infant weighing 1,940 Gm The heart blood contained 60 mg of dextrose per hundred cubic centimeters The organs were grossly normal The pancreas weighed 12 Gm Microscopically, the islands were not numerous, were generally fairly small and varied in size from masses containing a few cells to some with diameters of 262 by 208 microns The island cells and nuclei were of average size No mitotic figures were observed The intralobular and interlobular stromas were relatively prominent, were of loose texture and frequently contained large foci of hemopoietic cells Only an occasional eosinophilic myelocyte was noted The acinar cells and ducts appeared normal, but in places the acini appeared immature, with considerable intervening connective tissue

CASE 4—A septipara aged 30 had had diabetes since 1930 On Sept 10, 1931, by means of roentgen examination, she was thought to be in the seventh month of pregnancy Eleven samples of blood, taken at intervals from Sept 11, 1931 to Oct 2, 1931, included only a single specimen containing as high as 200 mg of

dextrose per hundred cubic centimeters. An elective induction was carried out at about term, and twins were delivered on October 2. The first baby, a boy, was delivered by version, because of a compound presentation (head and hand), and showed an uneventful course. The second baby, also a boy, was a footling, with the cord around his neck. The delivery was easy. There were two placentas. The second twin was somewhat blue when born. Rales developed in the lungs, and he died twenty hours after delivery.

The autopsy, performed three and one-half hours after death, showed a normally formed boy, weighing 2,800 Gm and measuring 46 cm from crown to heel. There was a tear in the left tentorium, with subtentorial hemorrhage. The lungs showed evidence of slight aspiration of amniotic fluid. The pancreas weighed approximately 5 Gm. Microscopically, the islands were moderately numerous and varied in size from masses containing a few cells to some with diameters of 262 by 239 microns. The island cells and nuclei were usually slightly larger and occasionally considerably larger than normal. The stroma surrounding the islands

TABLE 2 (Case 4)—*Chemical Examination of the Blood*

	Sugar, per Cent	Nonprotein Nitrogen, Mg per 100 Cc
Mother (at delivery)	0.17	25
Infant 1 (at delivery)	0.12	27
Infant 2 (at delivery)	0.11	28
Infant 1 (6¼ hr after birth)	0.10	
Infant 2 (6¼ hr after birth)	0.04, 0.05	
Infant 2 (heart blood 3½ hr post mortem)	0.03	78
Infant 1 (18 days after birth)	0.10	

was very slightly increased in amount and was in several instances moderately infiltrated with myelocytes, chiefly eosinophilic and mostly mature. There were other scattered minute foci of hemopoiesis. The acinar cells, ducts and blood vessels appeared normal.

CASE 5—A primipara aged 34 had had diabetes since Oct 1926. Her last catamenia was on June 22, 1934. She received unmodified insulin. Nine samples of blood, taken at intervals from Sept 18, 1934 to Feb 11, 1935, showed a single specimen containing 200 mg, another containing 210 mg and a third containing 230 mg of dextrose per hundred cubic centimeters. The remainder contained less than 200 mg per hundred cubic centimeters.

On February 11, 1935, a girl was born by classic cesarean section. One hour before delivery the mother's blood contained 230 mg of dextrose and 309 mg of cholesterol per hundred cubic centimeters, and the carbon dioxide-combining power was 28 volumes per cent, one-half hour after delivery the values were 160, 295, and 28, respectively. The infant's cord blood contained 130 mg of dextrose per hundred cubic centimeters, and the carbon dioxide-combining power was 24 volumes per cent. The baby was cyanotic, but its color improved with administration of oxygen. The course was marked by periods of cyanosis, poor respiration and occasional convulsions. The baby died nine and one-half hours after birth.

Autopsy, performed ten and one-half hours after death, showed a normally developed infant, weighing 3,020 Gm, with lividity of the dependent portions. The heart blood contained 60 mg of dextrose per hundred cubic centimeters. The lungs were atelectatic and microscopically showed evidence of aspirated amniotic fluid. The pancreas weighed 3 Gm, was reddish brown and appeared

normal Microscopically, there were numerous islands (fig 1), mostly large, which varied in size from masses containing a few cells up to some with diameters of 439 by 385 microns The island cells and nuclei were slightly larger than average, and there were occasional large nuclei, some of which were deeply chromatic Rarely, a mitotic figure was noted The stroma surrounding many of the islands was increased and densely infiltrated with eosinophilic myelocytes, mostly of the mature type There were a few foci of hemopoiesis within the stroma, which were not in association with the islands

CASE 6—A sextipara aged 37 had had diabetes since January 1932 Her first three deliveries, which were prior to the onset of diabetes, were uneventful The fourth, after the onset of diabetes, was normal, but the baby died on the tenth day from an umbilical infection The fifth was born by breech extraction and was very large The infant had been dead two weeks before delivery

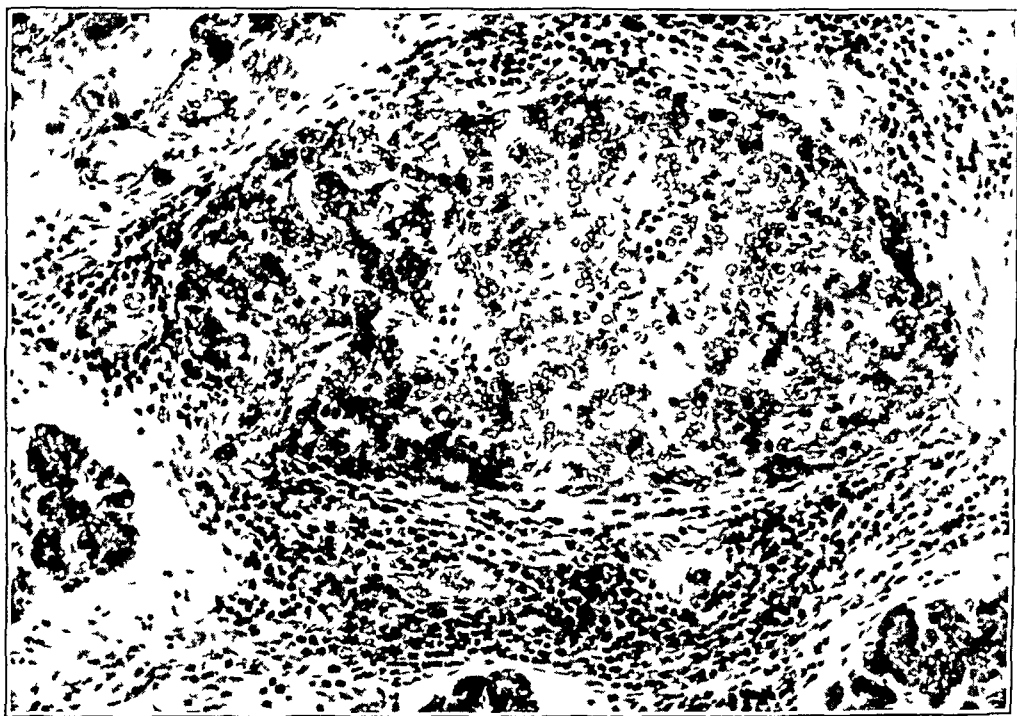


Fig 1 (case 5)—Hyperplasia of the islands of Langerhans, showing the infiltration of eosinophilic myelocytes and the comparative size of the accompanying acini (Stained with phloxine-methylene blue, $\times 189$)

The last catamenia of the sixth pregnancy was Dec 26, 1934 She received unmodified insulin Nineteen samples of blood, taken from Feb 2, 1935 to Sept 4, 1935, included a specimen which contained 200 mg and another which contained 230 mg of dextrose per hundred cubic centimeters, with the remainder containing below 200 mg per hundred cubic centimeters On Sept 4, 1935, a boy was delivered by classic cesarean section At delivery, the chemical findings of the mother's blood were normal, the sugar content being 130 mg per hundred cubic centimeters The cord blood contained 100 mg of dextrose per hundred cubic centimeters The baby exhibited intermittent periods of apnea A sample of blood taken twelve and one-half hours after birth contained 60 mg of sugar per hundred cubic centimeters The baby died suddenly, fourteen hours and ten minutes after birth

Autopsy, performed two and one-half hours after death, showed a well nourished infant, measuring 40 cm in length (crown to heel) and weighing approximately 3,500 Gm. The heart blood contained 120 mg of dextrose per hundred cubic centimeters, the liver blood, 180 mg. The lungs were atelectatic and microscopically showed evidence of aspirated amniotic fluid. The pancreas grossly was normal. Microscopically, there were numerous islands, many large, which varied in size from masses containing a few cells to some with diameters of 554 by 462 microns. The island cells and the nuclei were slightly larger than average, and the latter were occasionally extremely large and in a few instances deeply chromatic. In some cells the cytoplasm was more highly acidophilic than in others. Rarely, a mitotic figure was noted. The stroma surrounding some of the islands was infiltrated with eosinophilic myelocytes, mostly of mature type. Myelocytes were also present in small numbers within some of the islands. There were a few scattered hemopoietic cells within the stroma, not in relation with the islands.

CASE 7—A secundipara aged 33 had had diabetes for ten years prior to her second pregnancy. Her first pregnancy, two years previously, was terminated by a miscarriage at about seven weeks, during an attack of grip. Her last catamenia was on March 25, 1936. Diabetes was controlled by diet until September 1936, with the test for sugar in her premeal specimens of urine yielding reactions ranging from negative to an orange color with sediment. After September, she was given 24 units of insulin daily in a single morning dose. Fourteen samples of blood, taken at intervals from July 30, 1936 to Jan 28, 1937, included two samples containing 200 mg and one sample containing 240 mg of dextrose per hundred cubic centimeters, with the content of the remainder less than 165 mg per hundred cubic centimeters. On Jan 28, 1937, she was admitted to the hospital because of preeclampsia. Her blood pressure was 160 systolic and 104 diastolic. The urine contained albumin. The diabetes was controlled. On Jan 28, 1937, after she had received 2 ounces (60 cc) of orange juice with sugar two and three hours pre-operatively, a living girl was delivered by classic cesarean section. The mother's blood one hour after delivery contained 100 mg of dextrose per hundred cubic centimeters, and the cord blood contained 162 mg. The baby cried vigorously, but cyanosis was fairly marked, and the hands and feet were cold. The head was small. On the second day, slight cyanosis was present. The heart was large (confirmed by roentgen examination) and there was a systolic murmur, which was definite over the body of the heart but not present at the base or the apex. The edge of the liver was 7.5 cm below the costal margin. Forty-eight hours after delivery, the blood contained 57 mg of dextrose per hundred cubic centimeters. On the third day the baby became dusky, and there were irregular grunting respirations. The baby died sixty hours after birth.

Autopsy, performed five hours and fifty minutes after death, showed a well developed infant, weighing 3,898 Gm and measuring 49 cm in length (crown-heel). The heart showed cor triloculare biventriculare and hypertrophy. The liver weighed 170 Gm and was fatty. There was a bilateral bronchopneumonia. The pancreas weighed 3 Gm and appeared normal. Microscopically, there were numerous islands, generally of moderate size, which varied from masses containing a few cells to some with diameters of 346 by 254 microns. The island cells and nuclei were slightly larger than average. Some of the nuclei were very large and occasionally were deeply chromatic. Mitotic figures were rarely seen. The intralobular and interlobular stromas were not increased. In a few scattered foci, the stroma contained several hemopoietic cells and a few eosinophilic myelocytes, with indented round, or oval, or lobulated nuclei. Occasionally eosinophilic myelocytes were noted within the islands.

CASE 8—A quattuordecipara aged 39 was noted to have sugar in her urine Sept 3, 1936. The expected date of confinement was in November 1936. Of her previous pregnancies, nine resulted in full term normal deliveries, two in miscarriages at two and five months and two in stillbirths (the last, one year previous to the fourteenth pregnancy). Five samples of blood, taken from Oct 9, 1936 to Oct 28, 1936, contained from 95 mg to 164 mg of sugar per hundred cubic centimeters. The test of the urine for sugar gave positive results.

On Oct 29, 1936, a living girl was delivered normally. The baby cried but exhibited irregular movements. The scleras were slightly icteric. The reflexes were active and the neck slightly stiff. The baby nursed normally. During the first forty-eight hours the baby received only distilled water. A sample of blood then showed 42 mg of dextrose per hundred cubic centimeters. From the fifty-first to the fifty-eighth hour after birth, the baby took a 5 per cent solution of dextrose by mouth every hour. In the subsequent hour she was noted to be weaker, and at the fifty-ninth hour she was cyanotic. She was placed in an oxygen chamber. Respirations were of the Cheyne-Stokes type, and the heart beat was firm but slow. She died sixty hours after birth.

Autopsy, performed eighteen hours after death, showed a normally developed infant, weighing 3,930 Gm. The heart showed generalized hypertrophy (38 Gm). There was marked pulmonary hyperemia and edema. The right kidney exhibited thrombosis of the arcuate vessels, with acute necrosis and hemorrhage. One adrenal gland showed thrombosis and acute focal necrosis. The pancreas weighed 2 Gm and appeared grossly normal. Microscopically, there were a moderate number of islands, generally larger than normal, which varied in size from those of a few cells to masses containing diameters of 539 by 385 microns. The island cells generally were moderately enlarged, and the nuclei were often enlarged, some being twice the usual size. Mitotic figures were rare. Occasionally nuclei stained deeply chromatic. The stroma was not increased and appeared normal. There were only rare scattered hemopoietic cells, and eosinophilic myelocytes were rarely noted.

CASE 9—A primipara aged 36 dated the onset of her diabetes to July 1926. The date of her last catamenia was Feb 4, 1936. She was treated with unmodified insulin. Thirty-four samples of blood, taken at intervals from March 12 to October 19, included seven containing between 200 mg and 230 mg of dextrose per hundred cubic centimeters. Another sample, taken on October 19, after the intravenous administration of 1,000 cc of 10 per cent dextrose in physiologic solution of sodium chloride preparatory to a cesarean section, contained 290 mg per hundred cubic centimeters, and the carbon dioxide-combining power was 30 volumes per cent. The remainder contained less than 200 mg per hundred cubic centimeters.

On October 19 a dead girl was delivered by classic cesarean section. The baby was delivered with more difficulty than normal because of the tightness of the uterus and the size of the child (weight 10 pounds [4,536 Gm], born three weeks prematurely). The cord was flat and encircled the neck two or three times. The cord blood contained 120 mg of dextrose per hundred cubic centimeters, and the carbon dioxide-combining power was 18 volumes per cent. The membranes and the placenta were greenish gray. The baby had probably been dead for at least twenty-four hours, although the patient said she felt it the previous night.

The autopsy, performed three quarters of an hour after delivery, showed a normally developed infant, weighing 4,540 Gm. The heart blood contained 190 mg of dextrose per hundred cubic centimeters. The pancreas appeared normal. Microscopically, there were numerous islands (fig 2), many large, which varied in size from masses containing a few cells to some with diameters of 662 by 585 microns. The island cells and nuclei were moderately larger than average. Some of the nuclei were extremely large, and a few were deeply chromatic. Mitotic figures were rarely noted. The cytoplasm was acidophilic and in some cells greatly increased. The stroma, particularly in the vicinity of islands, was infiltrated with eosinophilic myelocytes, mostly of mature type. The stroma also contained scattered small foci of hemopoietic cells (fig 2).

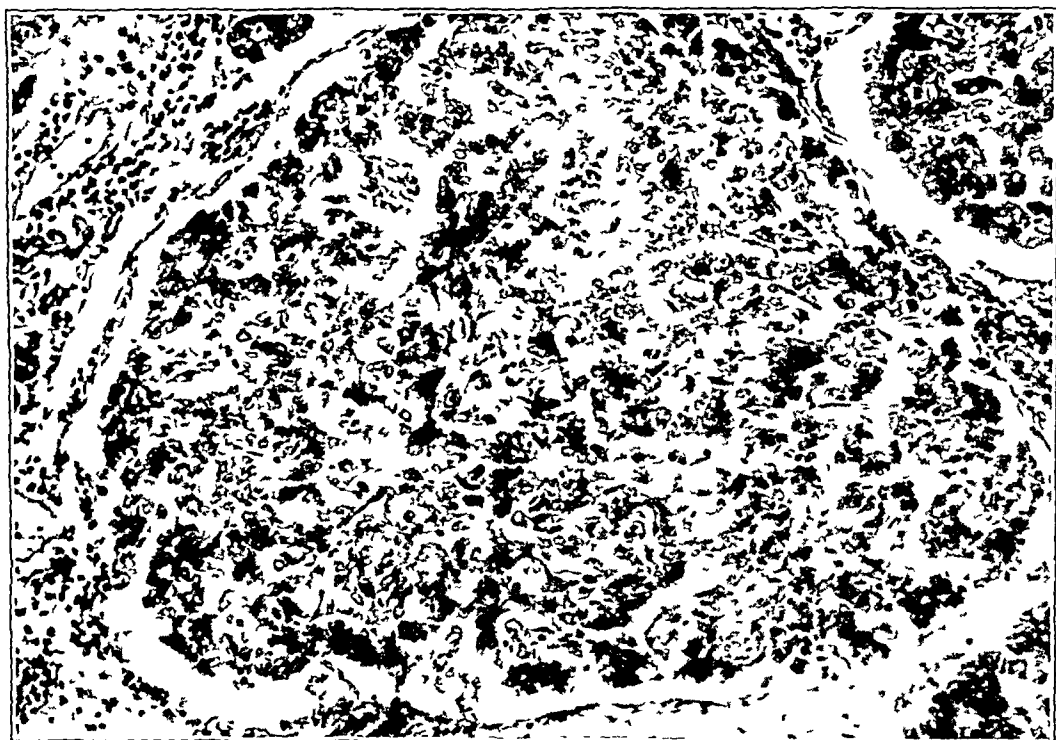


Fig 2 (case 9)—Hyperplasia of the islands of Langerhans (Stained with phloxine and methylene blue, $\times 189$)

COMMENT

The report of the chemical findings in the blood has been arranged according to the data available for study. Of the 9 infants of diabetic mothers, 4 infants (cases 3, 5, 6 and 9) had determinations of dextrose in the cord blood. In 2 infants (cases 3 and 5) the postmortem sugar content of the heart blood was lower than that of the cord blood, and in 2 infants (cases 6 and 9) it was higher, 1 of the latter 2 infants, however, was born dead. The postmortem blood (heart) sugar in the former 2 infants (cases 3 and 5) was 60 mg per hundred cubic centimeters, in each instance.

Case 4 was interesting because of twin births. The blood sugar content of the first twin at birth was 120 mg per hundred cubic centi-

TABLE 3—Data on Infants of Diabetic Mothers

Infants of Diabetic Mothers Measured	Number of Islands Measured	Mean Area of Islands in Square Microns	Standard Deviation of Mean Area of Islands	Diameters of Islands in Microns			Maximal Diameter of Any One Island	Weight of Baby	Weight of Pancreas	Duration of Pregnancy	Sex	Duration of Life of Baby
				Largest	Median	Smallest						
1	121	16,569	11,254	308 by 231	108 by 115	69 by 77	308	3 lb ½ oz	0.8 Gm	6 mo *	Male	Died shortly after birth 30 min
2	89	28,307	17,554	439 by 262	169 by 139	131 by 85	439	3 lb + *	2.5 by 4 cm not weighed	6 mo *	Male	6¾ hr
3	122	16,354	11,507	169 by 223	131 by 92	69 by 62	323	4 lb 4 oz	1.2 Gm	7 mo	Male	20 hr
4	87	21,631	12,631	262 by 239	154 by 123	92 by 77	308	6 lb 2½ oz	Approximately 5 Gm	8 mo	Male	9½ hr
5	82	57,017	35,738	439 by 385	285 by 239	115 by 115	477	6 lb 10 oz	3 Gm	Full term	Female	14 hr
6	88	76,183	49,645	554 by 462	254 by 231	108 by 100	570	7 lb 11 oz	Normal size 3 Gm	Full term	Male	60 hr
7	103	35,569	19,243	346 by 254	200 by 154	100 by 69	385	8 lb 12 oz	2 Gm	Full term	Female	72 hr
8	53	60,372	38,650	639 by 385	231 by 216	108 by 92	539	9 lb 8 oz	10 Gm ?	Full term	Female	Born dead
9	51	186,637	87,433	662 by 585	524 by 385	160 by 154	693	10 lb				

Infants of Diabetic Mothers	Cord	Blood Sugar		Dextrose Given to	
		In Life	Heart Post Mortem	Mother	Baby
1	Not taken	Not taken	Not taken	None	None
2	Not taken	Not taken	0.22	1,560 cc of 5% dextrose by clysis	None
3	0.16	0.11 and 0.06	0.06	None	None
4	Not taken	0.11, 0.04, 0.05	0.03	None	None
5	0.13		0.06	None	None
6	0.10	0.06	0.12	None	None
7	Not taken	0.062 and 0.057	Not taken	Orange juice with sugar	None
8	Not taken	0.042	Not taken	None	None
9	0.12		Not taken	None	None

* Estimated	0.19	1,000 cc of 10% dextrose intravenously	1 oz of 5% dextrose every hour after B S 0.42
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meters, at six and one-fourth hours after delivery, 100 mg per hundred cubic centimeters, and on the tenth day, 100 mg per hundred cubic centimeters. The baby's course was uneventful. The blood sugar content of the second twin at birth was 110 mg per hundred cubic centimeters, at six and one-fourth hours after delivery, 40 mg per hundred cubic centimeters and 50 mg per hundred cubic centimeters. The infant lived twenty hours, and a postmortem determination of the blood sugar, made three and one-half hours after death, showed 30 mg per hundred cubic centimeters. The autopsy revealed a subtentorial hemorrhage.

In case 8, a determination of the blood sugar at the forty-eighth hour revealed 42 mg per hundred cubic centimeters. In the succeeding ten hours, the baby received dextrose by mouth, with an apparent improvement in the general condition. However, her condition then grew rapidly worse, and she died at the fifty-ninth hour, before intravenous injections of dextrose could be given. No terminal or postmortem determinations of the content of blood sugar were made.

In case 7 the blood sugar content at birth was 62 mg per hundred cubic centimeters, and forty-eight hours later it was 57 mg per hundred cubic centimeters. No postmortem determination was made. The autopsy revealed congenital heart disease. In case 2, only a postmortem determination of blood (heart) sugar was made, it showed 220 mg per hundred cubic centimeters. In case 1, no determination of the blood sugar was made. Only 1 infant (case 8) received dextrose. The mother of 1 infant (case 2) was admitted in acidosis with pneumonia and received 1,500 cc of 5 per cent dextrose by clysis. The time of administration with relation to the time of delivery was uncertain.

The mother of 1 infant (case 7) received 2 ounces (60 cc) of orange juice with sugar at two and three hours previous to the cesarean section. The mother of another infant (case 9) received 1,000 cc of 10 per cent dextrose intravenously. The time of administration with relation to the time of delivery was uncertain.

Some investigators³ have shown that normally the value for fetal blood sugar is low, whereas others⁴ have found it to be about the same

3 (a) van Creveld, S. Carbohydrate Metabolism of Premature Infants. Blood Sugar During Fasting, *Am J Dis Child* **38** 912 (Nov) 1929. (b) McKittrick, J. B. Personal communication to the author.

4 (a) Rowley, W. N. Observations on the Blood Sugar During Pregnancy and the Puerperium, *Am J Obst & Gynec* **5** 23, 1923. (b) Morriss, W. H. The Obstetrical Significance of the Blood Sugar with Special Reference to the Placental Interchange, *Bull Johns Hopkins Hosp* **28** 140, 1917.

as the adult values McKittrick,^{3b} taking nearly simultaneous specimens of capillary blood, arterial cord blood and venous cord blood shortly after birth, found variations of 68 to 99 mg per hundred cubic centimeters, 86 to 102 mg per hundred cubic centimeters, and 83 to 99 mg per hundred cubic centimeters, respectively. Specimens of capillary blood taken at least three hours after the last feeding during the first fourteen days of life of 73 infants showed maximal daily values ranging from 93 to 160 mg per hundred cubic centimeters and minimal daily values ranging from 43 to 83 mg per hundred cubic centimeters. Morriss^{4b} reported an average of 115 mg per hundred cubic centimeters for infants' blood and 135 mg for maternal blood, and Rowley^{4a} reported averages of 110 mg per hundred cubic centimeters for maternal blood and 90 mg per hundred cubic centimeters for cord blood. Van Creveld^{3a} noted that blood sugar values obtained during fasting in the first month of the life of premature infants may be extremely low, and Schietter and Nevinny^{2a} noted low blood sugar values in normal infants for several days.

Of the blood sugar values obtained in this series the values in only 2 cases dropped below 60 mg per hundred cubic centimeters. One was 30 mg per hundred cubic centimeters, which occurred in a twin, autopsy revealed a subtentorial hemorrhage. The second twin had normal blood sugar figures and a normal course. In the other case a single determination, made on the third day, showed 42 mg per hundred cubic centimeters. No subsequent determination of blood sugar was made, and death was attributed to congestive heart failure. This may represent a case in which hypoglycemia was at least a contributory factor.

These cases, with the 2 possible exceptions, indicate that blood sugar levels are not abnormally low in the infants of diabetic mothers. In fact, it is possible that the high level of maternal blood sugar may raise the infant's blood sugar above the usual level, at least for a few hours.

In 7 of the 9 infants of diabetic mothers, the weights of the pancreas varied from 0.8 to 10 Gm, the latter probably being too high. Excluding case 9, in which the pancreas weighed 10 Gm and case 4, in which it was approximated at 5 Gm, the variation was from 0.8 Gm to 3 Gm. In 2 cases (1 and 3) the pancreas weighed 0.8 and 1.2 Gm, respectively, and in both instances the infants were born prematurely. In 6 newborn infants of nondiabetic mothers, none of which were born prematurely, Ogilvie⁵ found the weight of the pancreas to vary from 1.92 to 4.08 Gm. In my series of cases there is no definite evidence of an increase in the weight of the pancreases of infants of diabetic mothers.

5 Ogilvie, R. F. A Quantitative Estimation of the Pancreatic Islet Tissue, *Quart J Med* 6: 287, 1937.

In figure 3, the mean area of the islands per pound of body weight is calculated for infants both of diabetic and of normal mothers. Of the infants of nondiabetic mothers, excluding a single infant (case 9), the mean area of the islands ranged from 10,139 to 23,136 square microns, without any consistent correlation with weight. In case 9, there was a definite increase in the mean area of the islands, 35,715 square microns, and the cells appeared larger than average.⁶

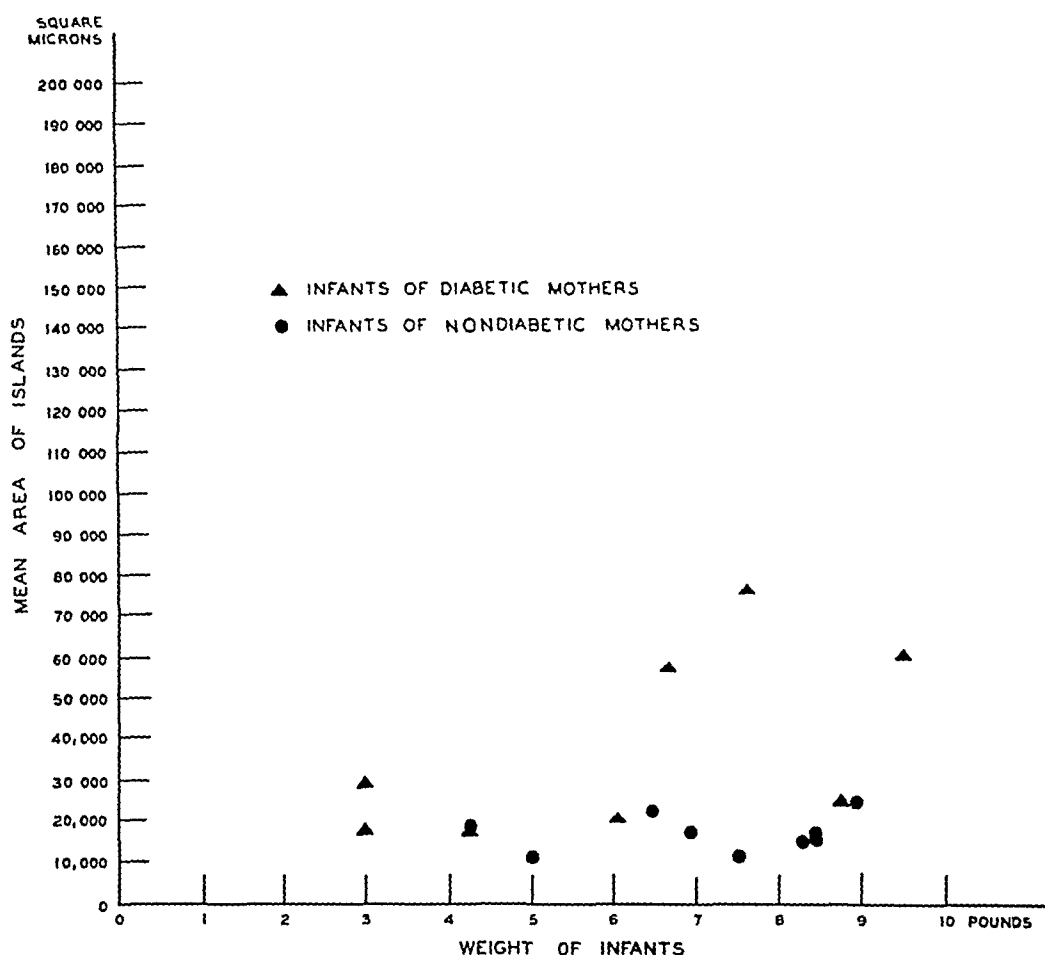


Fig 3—Mean area of the islands of Langerhans compared with the weight of infants born of diabetic and of nondiabetic mothers

6 No adequate chemical study has been made of either the mother or the infant, so it is possible that there may have been abnormal carbohydrate metabolism in either parent or child. However, the mother's tests showed no sugar in her urine, and so the mother may be presumed to have been nondiabetic at the time of delivery. The infant took lactose on several occasions.

The baby's color was intermittently poor, with cyanosis, frequent cries and twitching. Death occurred at the forty-second hour. Autopsy revealed considerable dilatation of the right side of the heart and passive congestion of lungs, liver and spleen. The peritoneal cavity contained 25 cc of clear yellow fluid. The brain was edematous.

In contrast to these, the pancreatic islands of infants of diabetic mothers had a mean area ranging from 16,354 to 186,637 square microns. Four of the infants of diabetic mothers had a mean island area larger than that of any of the control series. If the single infant with large islands in the control series (case 9) is excluded, there are 6 of the infants of diabetic mothers whose mean island area exceeds that of the infants of normal mothers. Of the 3 infants born of diabetic mothers whose mean island area falls within the range of that of the control series, 2 infants (cases 1 and 3) could be classed as prematurely born, and a third infant (case 4) was not fully developed, although the mean area of the islands in all 3 infants could be considered within the range of the mean area of the islands of the control group. Thus, there was a decided preponderance of large insular areas in the group born of diabetic mothers.

As will be noted by comparing the mean area of the islands with the maximum and minimal diameters of the islands, the mean area gives a much fairer picture. In general, the smaller islands, whether of infants of diabetic or of those of nondiabetic mothers, show less variation in the diameters, as would be expected, and the larger islands show a greater degree of variation. Even the minimal diameter of the islands of the infants of diabetic mothers is an appreciably greater diameter in most instances than the minimal diameter of those of the control series. In other words, not only are there single islands which are larger in the series of infants of diabetic mothers than in the control series, but in addition the maximal diameters of the islands tend to be greater, and the minimal diameters tend to be greater, thus it is shown that the hypertrophy and the hyperplasia involve not only scattered islands but nearly all the islands. These two series tend to differ both from the qualitative standpoint and from the standpoint of size of the islands of Langerhans, although there is some overlapping.

Microscopically, the infants of the control series, with the single exception that I described (case 9), exhibited an apparently average number of islands which were not increased in size. The island cells were not increased in size and appeared normal. The stroma occasionally contained minute foci of hemopoietic cells, in which only rarely an eosinophilic granulocyte could be identified. In a single infant among the control series (case 9), the islands appeared increased in number, and there was also an increase in size of some of the islands and the size of some of the cells and nuclei. The stroma rarely contained minute foci of hemopoietic cells, and rarely an eosinophilic granulocyte could be identified within or near an island. In 2 of the infants of diabetic mothers (cases 1 and 3) there was no apparent increase in the number of the islands, and the island cells did not appear enlarged. The stroma

in a single infant (case 1) showed a scattering of hemopoietic cells and rare eosinophilic granulocytes, particularly near the islands. In another infant (case 3) the stroma was tenuous, was relatively increased and contained large numbers of hemopoietic cells, including a few eosinophilic granulocytes. In 2 infants (cases 2 and 4) there appeared to be a slight increase in the number of the islands and a slight increase in the size of the cells. The nuclei were slightly enlarged, but occasionally they were much enlarged. The stroma was not appreciably increased. There were scattered minute foci of hemopoietic cells, and

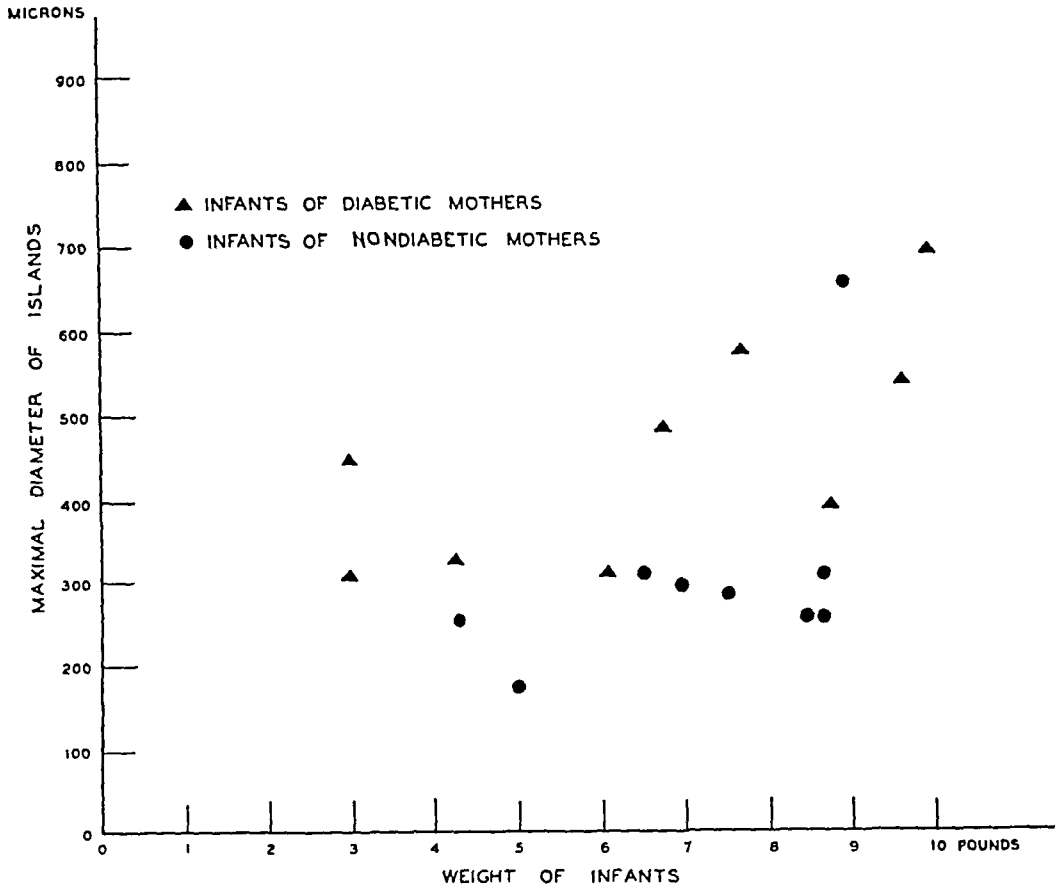


Fig 4—Maximal diameter of the islands of Langerhans compared with the weight of infants of diabetic and of nondiabetic mothers

particularly in the vicinity of some of the islands there were numerous eosinophilic granulocytes. In 5 infants (cases 5, 6, 7, 8 and 9) the islands generally appeared slightly increased in number, but this varied considerably with the different fields. The cells of the islands also generally appeared slightly to moderately enlarged, occasionally accompanied by large nuclei, most of which had a rather slight chromatin content, but occasionally the nuclei were deeply chromatic. Mitotic figures were rarely observed. The stroma was not increased and contained scattered minute foci of hemopoietic cells. In addition, in 3 infants (cases 5, 6 and 9), the stroma in the vicinity of some of the

islands, and to a less degree the stroma within the islands, contained eosinophilic granulocytes, most of which were mature. Two infants (cases 7 and 8) showed this infiltration to a much less degree.

Four of the infants born of the diabetic mothers had a mean insular area much higher than that of any born of the normal mothers. Six of the infants had an insular area larger than all but a single infant of the control series. The 3 infants of diabetic mothers that fell within the normal range were small infants, 2 of them being definitely premature. If instead of the mean insular areas the maximal diameter of any island is used (fig 4), only 1 infant of the group of diabetic mothers had an island greater than the largest of the islands in the control series (case 9). However, if case 9 is excluded, 7 of the infants of diabetic mothers had a maximal island diameter greater than that of the control series, and for 2 infants of diabetic mothers it was equal to that of the control series. While hemopoiesis may occur in the pancreatic stroma or in the peri-insular tissue of infants born of non-diabetic mothers, it is only in the group born of diabetic mothers that there is an appreciable eosinophilic infiltration. In this series of infants of diabetic mothers which I have observed, all showed it to a greater or less degree, but it was usually more prominent in the infants with more striking anatomic variations in size. These insular changes could not be correlated definitely with the variation in the carbohydrate metabolism of the mother. This lack of correlation was possibly due to the very few observations of the sugar content of the maternal blood that had been made. Unfortunately, there was no definite correlation between the variations in insular area and the variations in blood sugar level either during life or post mortem. However, all the infants for whom determinations of blood sugar were made during life, 5 in number, had had low values. In infants of nondiabetic mothers, there may be a comparable lowering of the blood sugar level.

The hyperplasia of the islands was probably a response to the diabetic state of the mother. Whether this hyperplasia was effected directly, through an increased demand for insulin because of elevated maternal and fetal blood sugar levels, or was brought about indirectly, through the pituitary body or other endocrine glands, cannot be said. I have no anatomic evidence to support the latter view.

SUMMARY AND CONCLUSIONS

The pancreases of 9 infants of diabetic mothers and of 9 infants of nondiabetic mothers were studied. The islands of Langerhans in the infants of diabetic mothers exhibited a variable degree of hypertrophy and hyperplasia, most marked in those infants nearing full term when they were born. The nuclei were frequently enlarged and occa-

sionally hyperchromatic. The stroma and to a less degree the islands of the infants of diabetic mothers frequently were infiltrated with eosinophilic granulocytes, many of which were mature. This infiltration of eosinophilic granulocytes was not present in the control group.

One infant in the control group, whose mother was not known to have diabetes, showed hypertrophy and hyperplasia of the islands and no obvious anatomic cause of death.

I am forced to conclude that some infants of diabetic mothers have definitely larger amounts of insular tissue than infants of nondiabetic mothers. This is particularly marked in those infants whose greater birth weights suggest a possible excess growth stimulus. On the other hand, it must be recognized that a fair number of the pancreases of infants of diabetic mothers will fall in the normal range of insular size.

The determinations of blood sugar on the whole show little correlation with insular size, the lowest level of blood sugar, 30 mg per hundred cubic centimeters, occurring in an infant dying of subtentorial hemorrhage, and one of the higher values, 190 mg per hundred cubic centimeters, occurring in a stillborn infant who had the largest islands of any in the series.

Dr Arthur T Hertig of the Boston Lying-In Hospital supplied the reports of cases 7 and 8, and Dr Herbert L Lombard of the Massachusetts Department of Public Health gave statistical advice.

ADJUSTMENTS IN CORONARY CIRCULATION AFTER EXPERIMENTAL CORONARY OCCLUSION

WITH PARTICULAR REFERENCE TO VASCULARIZATION OF
PERICARDIAL ADHESIONS

HOWARD B BURCHELL, M D

ROCHESTER, MINN

As disease of the coronary arteries plays such a dominant role in cutting short the productive age of man, it has long been the subject of study. The clinical observations of Morgagni, Rougnon, Heberden and Parry long preceded experimental studies on animals. During the middle of the nineteenth century several investigators, among whom were Erichsen,¹ Panum,² von Bezold and Breymann³ and Samuelson,⁴ observed the effects of ligation or embolism of the coronary arteries. The discussions were mostly concerned with the manner of the cardiac standstill, and the experiments were not designed for study of the collateral circulation in the heart. The greatest controversy arose over a manufactured term, "functional end artery," which was introduced by Cohnheim and von Schulthess-Rechberg⁵ in 1881. In the main, the difficulty arose between the anatomists, who could so clearly see the collateral vessels, and the experimental pathologists, who observed necrosis of the myocardium following ligation of the coronary arteries.

Kolster⁶ (1893) studied the production of myocardial infarction through its many stages, Baumgarten⁷ (1899) stated the belief that the

From the Division of Experimental Medicine, the Mayo Foundation

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1 Erichsen, J E. On the Influence of the Coronary Circulation on the Action of the Heart, London M Gaz **2** 561-564, 1842

2 Panum, P L. Experimentelle Beitrage zur Lehre von der Embolie, Virchows Arch f path Anat **25** 433-530, 1862

3 von Bezold, A, and Breymann, E, 1867, cited by Porter^{10a}

4 Samuelson, B. Ueber den Einfluss der Coronar-Arterien-Verschliessung auf die Herzaction, Ztschr f klin Med **2** 12-33, 1880

5 Cohnheim, J, and von Schulthess-Rechberg, A. Ueber die Folgen der Kranzarterienverschliessung fur das Herz, Virchows Arch f path Anat **85** 503-537, 1881

6 Kolster, R. Experimentelle Beitrage zur Kenntnis der Myomalacia cordis, Skandinav Arch f Physiol **4** 1-45, 1893

7 Baumgarten, W. Infarction in the Heart, Am J Physiol **2** 243-269, 1899

localization of infarction corresponded to the anatomic distribution of the arteries, but Hirsch and Spalteholz⁸ (1907), in a revolutionary paper, reported that there was no mortality following the ligation of the anterior descending artery in 8 dogs and 2 apes and that the region of infarction was smaller than the region supplied by this vessel. Miller and Matthews⁹ (1909), with the animals under ether anesthesia, were often able to ligate any one of the large coronary branches without immediate mortality, which is in striking contrast to the results reported by Cohnheim and von Schulthess-Rechberg and by Porter¹⁰ (1894).

Karsner and Dwyer¹¹ (1916) further studied myocardial infarction and drew attention to the irregular edge of the infarct as a probable indication of collateral circulation. Smith¹² (1918), in electrocardiographic studies of coronary occlusion, ligated large coronary branches with a relatively small mortality.

The accompanying table shows some of the results of experimental coronary occlusion. As the experiments were arranged for different purposes, as different anesthetics and varying methods of insufflation were used and as vessels probably were tied in different locations, a great variability in results is to be seen. It is unlikely that the heart exposed for hours would react similarly to one exposed for a few minutes in a rapidly executed surgical operation. Further clarification of differences in results is to be attributed to the work of Otto¹³ (1927), who showed that if the sympathetic nerves were intact the heart fibrillated after coronary occlusion, while if they had been cut an hour previous to the occlusion the heart dilated and stopped in diastole. A decrease in immediate mortality following ligation of coronary arteries after stellate ganglionectomy has been noted by Coelho and Rocheta¹⁴ (1929), Leriche

8 Hirsch, C, and Spalteholz, W. Coronararterien und Herzmuskel. Anatomische und experimentelle Untersuchungen, *Deutsche med Wchnschr* **20** 790-795 (May 16) 1907.

9 Miller, J L, and Matthews, S A. Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, *Arch Int Med* **3** 476-484 (June) 1909.

10 (a) Porter, W T. On the Results of Ligation of the Coronary Arteries, *J Physiol* **15** 121-138, 1894, (b) Further Researches on the Closure of the Coronary Arteries, *J Exper Med* **1** 46-70, 1896.

11 Karsner, H T, and Dwyer, J E. Studies in Infarction. IV. Experimental Bland Infarction of the Myocardium, Myocardial Regeneration and Cicatrization, *J M Research* **34** 21-39 (March) 1916.

12 Smith, F M. The Ligation of the Coronary Arteries. An Electrocardiographic Study, *Arch Int Med* **22** 8-27 (July) 1918.

13 Otto, H L. Ueber die Beziehungen der Accelerantes zu den Folgen der Unterbindung von Coronargefassen, *Arch f d ges Physiol* **217** 528-530, 1927, The Extracardial Nerves. IV. An Experimental Study of Coronary Obstruction, *Am Heart J* **4** 64-71 (Oct) 1928.

14 Coelho, E, and Rocheta, J. Recherches électrocardiographiques sur la ligature des artères coronaires chez le chien, *Compt rend Soc de biol* **102** 203-205, 1929.

Some Results of Ligation of the Coronary Arteries

Year	Investigator*	Animal	Vessel	Mortality, per Cent	Comment on Mortality Figures
1842	Erichsen ¹	Dog	Right coronary, circumflex	100	
1881	Cohnheim and von Schulthess-Rechberg ⁵	Dog	Circumflex, anterior descending	100	Curarized dogs
1893	Kolster ⁶	Dog	Last large branch of descending	Survived	
1894	Porter ¹⁰	Dog (67)	Circumflex descending	64	Cardiac arrest
			Right coronary	28	Only immediate mortality, not survival experiments, reported
			Septal	14	
			Anterior descending	0	Complete recovery without disability
1907	Hirsch and Spalteholz ⁸	8 dogs 2 apes		Survived	
1909	Müller and Matthews ⁹	Dog	Circumflex	87	Cardiac arrest
			Anterior descending	0	Only immediate mortality reported
1918	Smith ¹²	Dog (66)	Circumflex	57	Immediate mortality
			Anterior descending	9	Surviving dogs examined three to eight weeks after operation
			Right coronary	54	Complete heart block
1928	Lauterbach, W. Ztschr f d ges exper Med 61 655-686, 1928	Dog (7)	Septal		
1929	Cochlo and Rocheta ¹⁴	Dog	Anterior descending	High 100 Low 0	All dying with ventricular fibrillation, less rapid in onset with ligation of right coronary artery
			Posterior descending	100	
			Right coronary	100	
			Circumflex, anterior descending, right coronary	100	Fibrillation, low ligations have permitted survival
1930	Clerc, A., Deschamps, P. N., Bascourt, M., and Levy, J. R. Compt rend Soc de biol 103 223-226, 1930	Dog	Anterior descending	54	Immediate mortality in the first hour from ventricular fibrillation
1931	Fell, H. S., Katz, L. N., Moore, R. A., and Scott, R. W. Am Heart J 6 522-535 (April) 1931	Dog (26)	Anterior descending		Recovery usually
1932	Barnes, A. R., and Mann, F. C. Am Heart J 7 477-497 (April) 1932	Dog	Posterior descending		
1933	Leriche and Fontaine ¹⁵	Dog	Anterior descending	High ligation 100, low, rare	Immediate mortality with fibrillation, rupture of heart reported in later stages
1933	Parade, G. W. Ergebn d inn Med u Kinderh 45 337-432, 1933	Dog	Circumflex Descendens	100	Immediate fibrillation, no figures for total mortality of all dogs
1933	Wood, F. C., and Wolfarth, O. C. Arch Int Med 51 771-778 (May) 1933	Dog	Right coronary	Most survive Some survive	"Ventricular fibrillation is the usual terminal event in experiments on coronary occlusion, occurring most rapidly when circumflex is obstructed"
1935	Beck and Tichy ²¹	Dog	Right coronary	Poorly tolerated	Total mortality for "normal" animals
1936	Cox and Robertson ¹⁰	Dog (10)	Anterior descending	50	Immediate mortality with fibrillation
1936	Harris, B. R., and Hussey, R. Am Heart J 12 724-735 (Dec) 1936	Dog	Anterior descending	58	
1936	de Waart, A., Storm, O. J., and Koumans, A. K. J Am Heart J 11 676-704 (June) 1936	Monkey	Anterior descending	53†	Total mortality, fibrillation usually with ligation of left vessel, less frequently with ligation of right
1937	Gross, L., Blum, L., and Silverman, G. J. Exper Med 65 91-108 (Jan) 1937	Dog	Right coronary	46†	
			Anterior descending	53	24 hour mortality

* Superior figures following the name of investigator refer to footnotes in the text
† Calculated from authors' table

and Fontaine¹⁵ (1933), Cox and Robertson¹⁶ (1936) and Schauer, Gross and Blum¹⁷ (1937)

PERICARDIAL ADHESIONS AS A SOURCE OF BLOOD SUPPLY TO THE HEART

Thorel¹⁸ (1903) suggested that in a case of closure of both coronary arteries the heart might have received a blood supply through vessels in pericardial adhesions. Merkel¹⁹ (1907) referred again to the possibility of blood entering the heart through adhesions, but in neither of these instances did the discussion go beyond the suggestion of that possibility.

Moritz, Hudson and Organ²⁰ (1932) demonstrated in 4 hearts with partial or complete obliteration of the pericardial sac by fibrous adhesions that after injection of the coronary arteries with a colloidal suspension of lampblack there was rich injection of the vessels of the parietal pericardium in all cases. In none of the 4 cases were the coronary arteries significantly diseased.

After the observations of Moritz, Hudson and Organ, Beck and Tichy²¹ reported that in February 1932 they had begun experiments in which adhesions of the heart to various structures were produced and the vascularization was studied by the injection of an aqueous solution of ferric ferrocyanide. Portions of the parietal pericardium, mediastinal tissues, omentum and skeletal muscle were used as grafts on the heart. The following main conclusions were reached: (1) Total occlusion of the right coronary artery or partial occlusion of several coronary vessels was better tolerated if, through adhesions, a collateral vascular bed had been prepared for the heart, (2) in only a few experiments did infarction supervene when pericardial adhesions had been previously produced, and (3) vascularization from a collateral bed varied more or less directly with the extent of the constriction of the main coronary vessels. The authors emphasized that in one of the experiments about 85 per cent

15 Leriche, R., and Fontaine, R. *Chirurgie des nerfs du coeur*, Acta chir Scandinav **70** 260-284, 1933

16 Cox, W. V., and Robertson, H. F. Effect of Stellate Ganglionectomy on the Cardiac Function of Intact Dogs and Its Effect on the Extent of Myocardial Infarction and on Cardiac Function Following Coronary Artery Occlusion, Am Heart J **12** 285-300 (Sept) 1936

17 Schauer, G., Gross, L., and Blum, L. Hemodynamic Studies in Experimental Coronary Occlusion. Stellate Ganglionectomy Experiments, Am Heart J **14**:669-676 (Dec) 1937

18 Thorel, C. Pathologie der Kreislauforgane, Ergebn d allg Path u path Anat **91** 559-1116, 1903

19 Merkel, H. Zur Kenntnis der Kranzarterien des menschlichen Herzens, Verhandl d deutsch path Gesellsch **11** 127-131, 1907

20 Moritz, A. R., Hudson, C. L., and Organ, E. S. Augmentation of the Extracardiac Anastomoses of the Coronary Arteries Through Pericardial Adhesions, J Exper Med **56**:927-931 (Dec) 1932

21 Beck, C. S., and Tichy, V. L. The Production of a Collateral Circulation to the Heart. I. An Experimental Study, Am Heart J **10** 849-873 (Oct) 1935

of the total cross sectional area of both coronary arteries was shut off with maintenance of the animal's health

Some modifications of these conclusions were published by Mautz and Beck,²² particularly in respect to the inherent ability of anastomotic channels in the heart to enlarge and prevent infarction when a large coronary branch was slowly occluded. However, they expressed the opinion that in some instances, in which the potentialities of the collateral vessels in the heart were not as great, there existed a favorable gradient of pressure across the newly formed vessels in the adhesions and that these enlarged and persisted, to function as carriers of blood to the heart.

O'Shaughnessy²³ stated that in 1933 he had been attracted by the ability of the omentum to increase in vascularity and had begun a series of experiments on cats and dogs, in which pedicled omental grafts were applied to the heart. He reported that vascular communications arose between the omentum and the myocardium without destruction of the epicardium and irrespective of whether the coronary vessels were occluded. O'Shaughnessy placed considerable emphasis on experiments in which greyhounds that had been subjected to ligation of the anterior descending artery were apparently benefited in their tolerance to exercise by the application of an omental graft to the heart.

Moia and Acevedo²⁴ observed that when pericardial adhesions were produced between the heart and the mediastinum, the muscle tissue or the great omentum, vascular connections were produced. These communications appeared as early as two or three weeks after operation and were demonstrated by the injection of dye into the graft and its appearance in the coronary vessels.

Lezius²⁵ studied the vascularity of the adhesions between the lung and the heart. He observed that vascular connections were regularly produced and stated the belief that the blood flow was toward the myocardium. He expressed the opinion that hearts in which the right and left coronary arteries had been ligated remained completely efficient by reason of a *Kardiopneumopexie*, which supplied blood sufficient both in quality and in quantity.

22 Mautz, R. R., and Beck, C. S. Augmentation of Collateral Coronary Circulation by Operation, *J Thoracic Surg* **7** 113-131 (Dec.) 1937.

23 O'Shaughnessy, L. An Experimental Method of Providing a Collateral Circulation to the Heart, *Brit J Surg* **23** 665-670 (Jan.) 1936. Surgical Treatment of Cardiac Ischaemia, *Lancet* **1** 185-194 (Jan. 23) 1937.

24 Moia, B., and Acevedo, H. J. El tratamiento quirúrgico de la insuficiencia coronaria por la provocación artificial de una circulación colateral al corazón, *Rev argent de cardiología* **3** 225 (July-Aug.) 1936, abstracted, *Ztschr f Kreislaufforsch* **29** 703-704 (Sept. 15) 1937.

25, Lezius, A. Die anatomischen und funktionellen Grundlagen der künstlichen Blutversorgung des Herzmuskels durch die Lunge bei Coronararterienverschluss, *Arch f klin Chir* **191** 101-139, 1938.

Grassi²⁶ studied the results of placing muscle grafts on the hearts of rabbits. In the majority of his experiments the left coronary artery was ligated at the same operation. Vascular communications were demonstrated, and he apparently concluded that the reestablishment of the cardiac circulation was through utilization of these vessels in the pericardial adhesions.

CRITICAL ANALYSIS OF THE LITERATURE

Many of the facts pertaining to the possible function of adhesions as a mechanism of blood supply require more intense scrutiny. In particular, it is essential that the differentiation between the presence of vascular connections and the actual blood flow should be further clarified. This potential blood supply, seen most dramatically when pericardial adhesions are separated in the operating room, awaits proof of its adequacy and the direction of flow of the blood.

For the enlargement of collateral channels, it would seem a requisite that a gradient of pressure across them should exist. In theory, if the vascular network produced in the healing process between the heart and another tissue is to persist and to form enlarging collaterals, the coronary vessels would need to be constricted. Beck and Tichy²¹ and Mautz and Beck²² expressed the belief that the results of their experiments were entirely in support of this supposition. With the coronary vessels intact, it is theoretically possible that in the period of isometric contraction and in the fraction of a second between the rise of systolic pressure in the coronary and that in the peripheral arteries conditions might be favorable for blood to flow away from the heart.

It has been stated that when the coronary vessels were constricted to a certain extent the coronary flow was similarly diminished. This must be an erroneous assumption, particularly when the length of the constriction is small. Mann, Herrick, Essex and Baldes²⁷ have shown that the internal diameter of a vessel may be decreased to half its original diameter over a distance of 8 to 10 mm without a significant reduction in the volume of blood passing through the vessel.

Robertson²⁸ expressed the opinion that in successive operations he was finally able to tie off the trunks of the main vessels, an operative feat which is somewhat open to question. He concluded that a number

26 Grassi, A. Contributo sperimentale allo studio del ristabilimento della circolazione cardiaca a mezzo di muscolo vitale previa legatura delle coronarie, *Arch ital di chir* **47**:234-252, 1937.

27 Mann, F. C., Herrick, J. F., Essex, H. E., and Baldes, E. J. Effect on Blood Flow of Decreasing Lumen of Blood Vessel, *Surgery* **4**:249-252 (Aug) 1938.

28 Robertson, H. F. The Reestablishment of Cardiac Circulation During Progressive Occlusion of the Coronary Arteries. An Experimental Study on Dogs, *Am Heart J* **10**:533-541 (April) 1935.

of hearts were nourished through pericardial adhesions and that he saw regions of heart muscle "obviously infarcted" after separation of the adhesions. What would be the appearance of the heart leading to such a conclusion is not readily conceived.

O'Shaughnessy,²⁸ in his illustration of perfusion of an omental graft, showed surprisingly large quantities of the perfusate issuing from the aorta, but no actual figures for the quantity were given.

Lezius²⁵ showed convincing roentgenograms of hearts after injection through the pulmonary artery, the most important part in the procedure being the use of a capillary-passing substance, a colloid suspension of thorium dioxide. His experiments, designed to show the direction of flow in the pulmonary-cardiac adhesions, seem inconclusive. He stated the belief that in 2 instances ligation of the main bronchus, including the bronchial arteries, rendered the graft ineffective.

It is not my intention in this paper to discuss the results of the operations for coronary sclerosis in man. The preliminary reports of Beck,²⁹ of Beck and Tichy,²¹ of Feil and Beck,³⁰ of O'Shaughnessy,²³ of Davies, Mansell and O'Shaughnessy,³¹ of Griffith and Bates³² and of Moia and Acevedo²⁴ may be mentioned, and the final complete reports of the patients whose condition has been bettered will be most interesting.

ANATOMIC RELATIONS OF THE CORONARY ARTERIES OF THE DOG

While the general configuration of the coronary architecture in the dog has long been known, certain variations from the human arrangement have not always received sufficient emphasis. The coronary vessels in the dog's heart were restudied by dissection and by roentgenographic methods, the observations were similar in general to those of Baumgarten,⁷ of Spalteholz,³³ of Meek, Keenan and Theisen³⁴ and of Moore³⁵.

29 Beck, C. S. Further Data on the Establishment of a New Blood Supply to the Heart by Operation, *J Thoracic Surg* **5** 604-611 (Aug) 1936.

30 Feil, H., and Beck, C. S. The Treatment of Coronary Sclerosis and Angina Pectoris by Producing a New Blood Supply to the Heart, *J A M A* **109** 1781-1786 (Nov 27) 1937.

31 Davies, D. T., Mansell, H. E., and O'Shaughnessy, L. Surgical Treatment of Angina Pectoris and Allied Conditions, *Lancet* **1** 1 (Jan 1), 76 (Jan 8) 1938.

32 Griffith, G. C., and Bates, W. Heart Surgery. Ventricular Perforation in Transplanting a New Blood Supply, *Internat Clin* **2** 17-28 (June) 1938.

33 Spalteholz, K. W. Die Arterien der Herz wand. Anatomische Untersuchungen an Menschen- und Tierherzen nebst Erörterung der Voraussetzungen für die Herstellung eines Kollateralkreislaufes, Leipzig, S. Hirzel, 1924.

34 Meek, W. J., Keenan, M., and Theisen, H. J. The Auricular Blood Supply in the Dog. General Auricular Supply with Special Reference to the Sino-Auricular Node, *Am Heart J* **4** 591-599 (June) 1929.

35 Moore, R. A. The Coronary Arteries of the Dog, *Am Heart J* **5** 743-749 (Aug) 1930.

It is deemed desirable to draw attention again to certain features. The left coronary artery divides within 2 to 4 mm into its descending and its circumflex branch, making experimental occlusion of its main stem practically impossible. A large septal branch arises from the region of bifurcation and runs backward and to the right into the muscular septum. The diameter of this vessel is usually about two-thirds that of the anterior descending branch, but in occasional instances it may be as large as the latter.

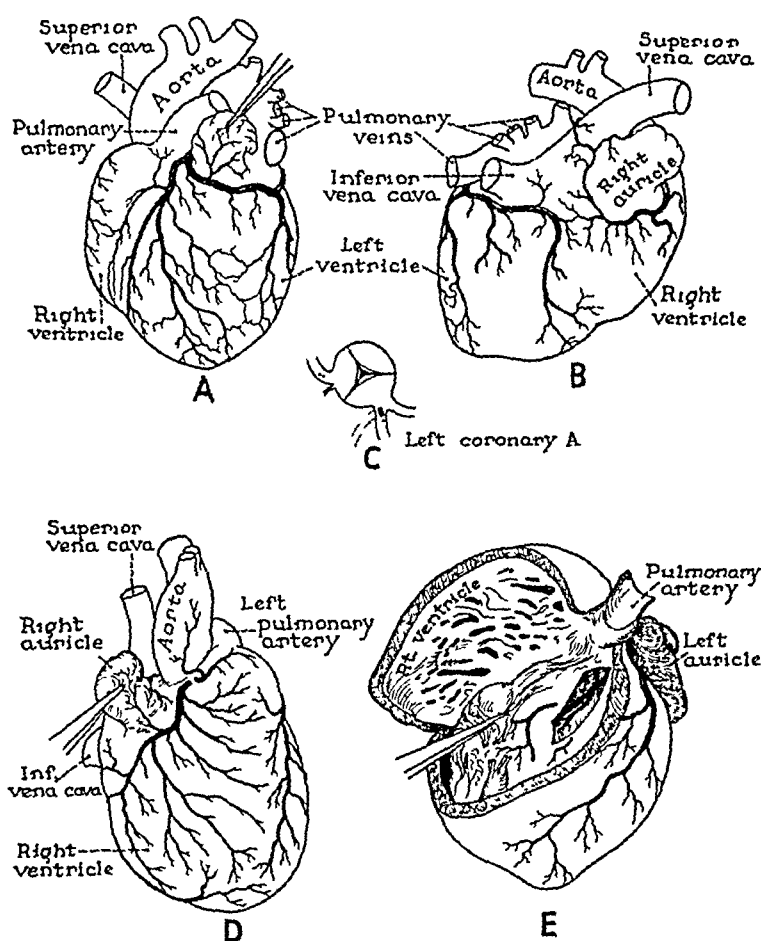


Fig 1—Dog's heart, showing distribution of the coronary arteries. *A*, anterior aspect, *B*, posterior aspect, *C*, schematic drawing of the origins of the vessels, showing an accessory right coronary artery, the origin of the septal branch and the numerous small branches arising in the first portions of the arteries, *D*, acute marginal aspect, and *E*, view of the course of the septal branch as seen by opening the right ventricle and partially dissecting the septum.

The posterior descending artery is derived uniformly from the left circumflex vessel. There is generally a variably sized vessel, arising from the anterior descending artery, which crosses the anterior inter-ventricular groove and runs downward on the right ventricle, parallel to its parent vessel.

The auricular branches show considerable variability, but the left proximal branch and the right distal branch are generally the largest and

the most constant. Occasionally, a branch from the middle portion of the right coronary artery seems to replace the distal branch as respects size and distribution (fig 1)

The anastomoses between the coronary vessels are readily demonstrated to be numerous, as has been stated by Spalteholz³³ and by Moore³⁵. The anastomosis of the left proximal and the right distal auricular branches in the region of the ostium of the superior vena cava has been a constant observation. While innumerable anastomotic channels can be demonstrated on the surface of the heart when the coronary arteries are injected with india ink (fig 2), only a small proportion of these have appeared on the normal heart when the injection mass has contained barium sulfate (plain suspension or Gross's³⁶ or Schles-

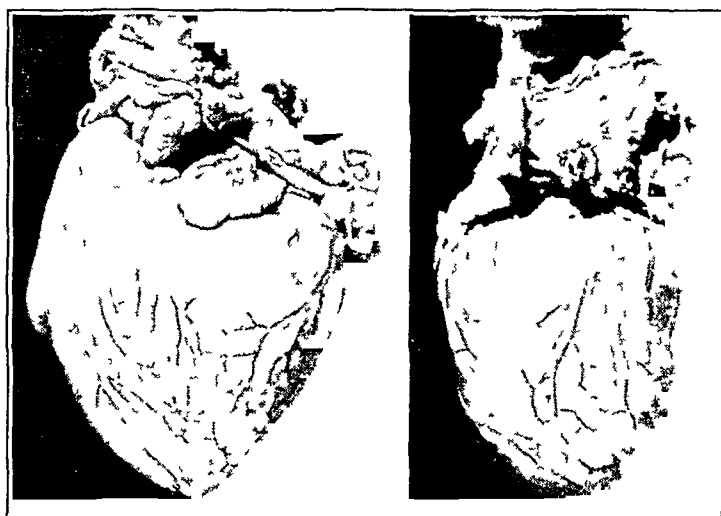


Fig 2—Anterior and obtuse marginal aspects of a normal dog's heart, showing anastomoses, after injection of a mixture of agar and india ink

inger's³⁷ mixture). More numerous collateral channels are visible on the anterior surface, since posteriorly the large coronary branches pass into the myocardium more rapidly. Though the muscle bundles have not been dissected out, it has been difficult to believe from this study that they could have a specific blood supply.

When the heart in situ was injected with india ink, small anastomotic channels leaving the heart along the pulmonary veins and superior vena cava, and to a lesser extent along the inferior vena cava, were readily demonstrated. The vasa vasorum of the aorta were also injected, and in 1 instance, in an injection of a right accessory coronary artery, the

36 Gross, L. *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects*, New York, Paul B Hoeber, 1921.

37 Schlesinger, M. J. An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *Am Heart J* **15** 528-568 (May) 1938.

materials flowed from a large vasa vasorum about 4 cm above the aortic orifice. These observations are in accord with those of Spalteholz,³⁸ of Woodruff³⁸ and of Hudson, Moritz and Weain³⁹

REESTABLISHMENT OF THE CIRCULATION AFTER CORONARY OCCLUSION

For observations on the development of both intracardiac and extracardiac anastomoses it would be ideal to have a method by which vessels could be slowly occluded over much of their length. Such an ideal has not been achieved, and it is necessary to preface the reports on the experiments with the statement that if one had had a perfect method of producing a replica of coronary disease, it might have been observed that the anastomotic vessels had different arrangements, and perhaps that the extracardiac supply was more greatly augmented.

In one series of experiments, constricting collars, having an internal diameter of 1.5 to 2.5 mm and a length of 6 to 8 mm, were placed on the three main coronary vessels in two operations, about two weeks apart. In the animals that survived the first week, no evidence of any disability was manifest, and their tolerance to exercise on a sloping treadmill seemed equal to that of normal animals. Three animals died suddenly in the period from the third to the fifth day, at a time when they were active and showed every evidence of excellent recovery from the operation. At autopsy the lumens of the constricted vessels were patent and myocardial infarction was absent.

In some instances silver clips were used to constrict the coronary vessels, and unless the constriction was originally severe, the stenosis did not progress. It was thought possible that different types of metal might produce a greater tissue reaction, as has been indicated by the study of the reaction of tissue to metal prostheses in bone surgery (Venable, Stuck and Beach⁴⁰). Clips of silver, aluminum, copper, steel and nickel were used, without any constant difference in the extent of tissue reaction. When two metals were used close together in a constricting collar, there was an increased proliferation of fibrous tissue, and small necrotic foci were seen microscopically. In 1 instance a localized focus of necrosis in the arterial wall with acute thrombosis of the vessel was observed, but this was a curiosity. As a rule, in spite of inflammatory tissue around the vessel having a radius up to 1 cm there was no evidence of progression in the constriction. The observations on the use of metal

38 Woodruff, C. E. Studies on the Vasa Vasorum, *Am J Path* **2** 567-569, (Nov.) 1926

39 Hudson, C. L., Moritz, A. R., and Weain, J. T. Extracardiac Anastomoses of the Coronary Arteries, *J Exper Med* **56** 919-925 (Dec.) 1932

40 Venable, C. S., Stuck, W. G., and Beach, A. The Effects on Bone of the Presence of Metals, Based upon Electrolysis. An Experimental Study, *Ann Surg* **105** 917-938 (June) 1937

bands are in accord with those of Halsted,⁴¹ who, having placed constricting bands on the aortas of dogs, found that it was only when the lumen was almost, but not quite, occluded by the band that complete occlusion subsequently occurred

With simple constrictions of the coronary vessels, there was frequently demonstrable a cuff of vessels bridging the constriction. These vessels lay in the fat of the auriculoventricular groove and, microscopically were seen to be small, thick-walled arteries. In some instances in which the proliferation of fibrous tissue was extensive, small, newly formed vascular channels acted as bridges across the constriction.

For the production of chronic occlusion, a method was evolved which proved more efficacious than any other. If a constricting collar of one

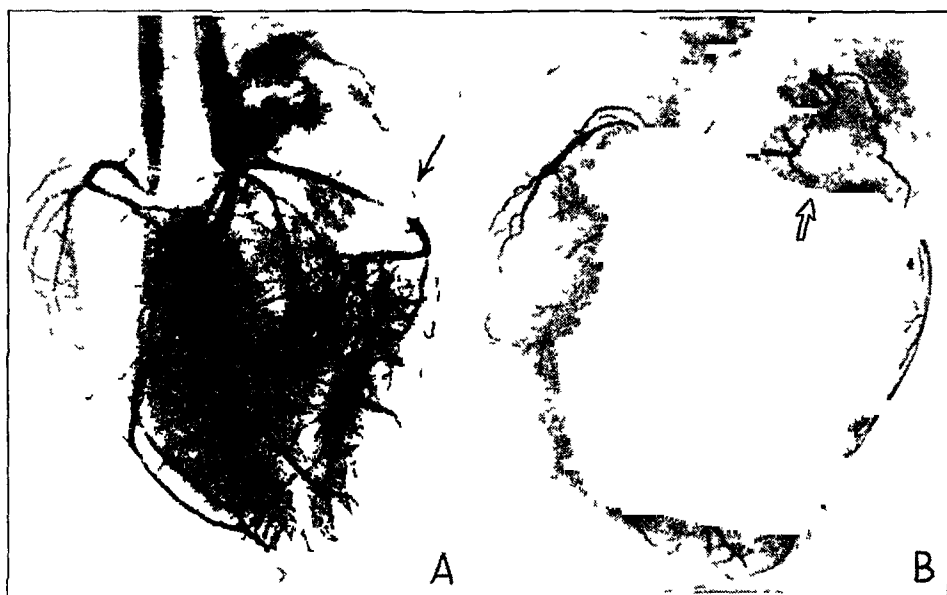


Fig 3—Two hearts after occlusion of the circumflex branch of the left coronary artery. *A*, after acute ligation, *B*, chronic occlusion accomplished by metal collar which has completely sloughed out. In the heart shown in *A* there was a myocardial scar in the posterior wall of the left ventricle, but in that shown in *B* the myocardium of all the ventricular walls was normal. Note the auricular and ventricular anastomoses in *B*. The arrows indicate the points of occlusion.

metal or of a combination of metals was placed on a vessel and was loosely attached to a rib with a linen thread, it was found that complete obstruction of the vessel would occur in many instances without the production of myocardial infarction (figs 3 and 4). If severe constrict-

41 Halsted, W. S. The Results of Complete and Incomplete Occlusion of the Abdominal and Thoracic Aortas by Metal Bands, *J. A. M. A.* **47**: 2147-2148 (Dec 29) 1906.

tion of the coronary artery had been produced, it was found that ligation could later be carried out with minimal infarction (fig 4)

By the combination of these methods, the right coronary artery and the circumflex and anterior descending branches of the left coronary artery have been occluded in successive stages without the production of infarction and with the maintenance of normal cardiac function (fig 5)

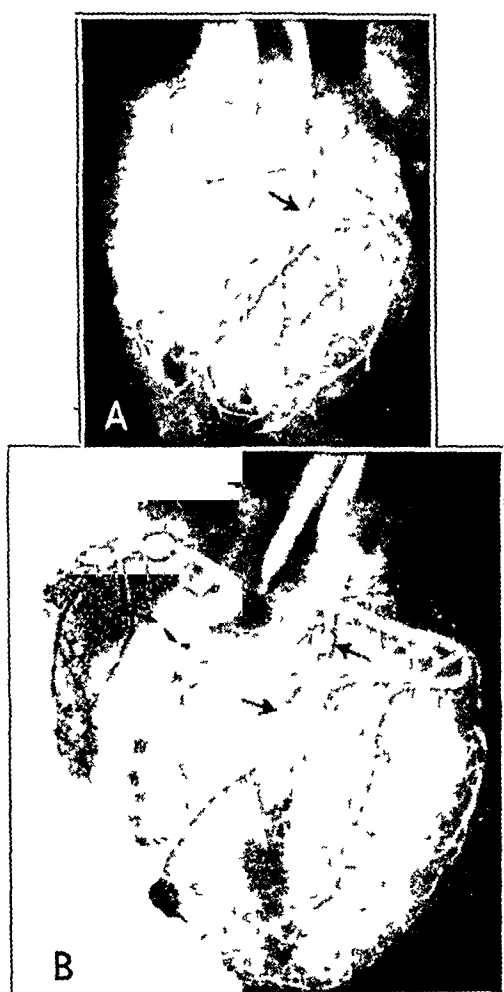


Fig 4—Two hearts after ligation of the anterior descending branch of the left coronary artery, (*A*) without a preceding period of constriction and (*B*) after a preceding period of constriction. Both animals recovered completely. There was a large myocardial scar in the heart shown in *A* and in the heart shown in *B* a very small one. In *A* the right coronary artery has also been ligated, in *B* a branch on the obtuse margin has been ligated, and constricting clips have been placed on the right coronary artery. In *A* the arrow indicates the point of ligation, in *B* the upper arrow indicates the constricting collar, and the lower arrow, the point of ligation.

In dogs that have survived the immediate effect of ligation of the anterior descending branch or the circumflex branch, there is little or no evidence of cardiac disability after the infarct has healed. The scar of

the previous infarction varies greatly in size and rarely involves the whole thickness of the wall, more often the wall retains some myocardial tissue, particularly toward its outer surface. When the left circumflex branch has been ligated and the dog survives, the resulting infarction severely involves the posterior papillary muscle, which has been observed to be completely infarcted and on one occasion ruptured, and as a late result to be represented only by a small scarred mass, to which the chordae tendineae were attached.

In rare instances, a dog may survive acute ligation of the anterior descending, circumflex and right coronary arteries, when these are not tied too close to their origins, in successive operations. One such dog seemed to be capable of normal activity in spite of two large scars in the left ventricle, which were observed later on postmortem examination (fig 6).



Fig 5—Two hearts that had recovered from occlusion of the right coronary artery and of the circumflex and anterior descending branches of the left coronary artery. In *A* the arrows indicate where the right coronary artery and the circumflex branch of the left coronary artery had been occluded by metal bands and where the anterior descending branch of the left coronary artery had been ligated. In *B* the arrows indicate where the right coronary artery had been destroyed by metal bands, where the circumflex branch of the left coronary artery had been occluded by a band, which had sloughed away, and where the descending branch of the left coronary artery had been ligated after a period of constriction by a metal band. No macroscopic scar was observed in either heart. Microscopically, small regions of fibrosis in the anterior wall of the ventricle were seen in the heart shown in *A*, normal myocardium was observed in the heart shown in *B*.

SITES OF ANASTOMOSES

In experimental occlusions of the coronary arteries, it is axiomatic that the peripheral portion of the occluded vessel will be utilized in the reestablishment of the blood flow. When either the circumflex or the anterior descending branch is occluded the main site of anastomosis is

usually on the surface of the left ventricle. When the circumflex branch has been obstructed a large anastomotic channel may sometimes be demonstrated between the right coronary and the left circumflex artery, at the crux of the heart (fig 7), designated by Kugel⁴² as that portion of the heart in which the two auricles and the two ventricles meet. Usually the anastomoses in this region are very small and play a negligible role in the collateral circulation (fig 8). With occlusion



Fig 6—A heart after successive ligations of the right coronary artery and of the circumflex and anterior descending branches of the left coronary artery, with recovery. In the cross sections the posterior wall of the ventricle lies to the left. Note the complete injection of the arterial tree. Note maintenance of the thickness of the ventricular wall in spite of the scars of the infarcted regions.

of the anterior descending artery, the anterior branches from the right coronary artery are frequently enlarged but rarely show communications with the anterior descending artery that will contain a barium mixture. With occlusion of the right coronary vessel, except for the auricular

⁴² Kugel, M. A. Anatomical Studies on the Coronary Arteries and Their Branches. I. Arteria Anastomotica Auricularis Magna, *Am Heart J* 3:260-270 (Feb.) 1928.

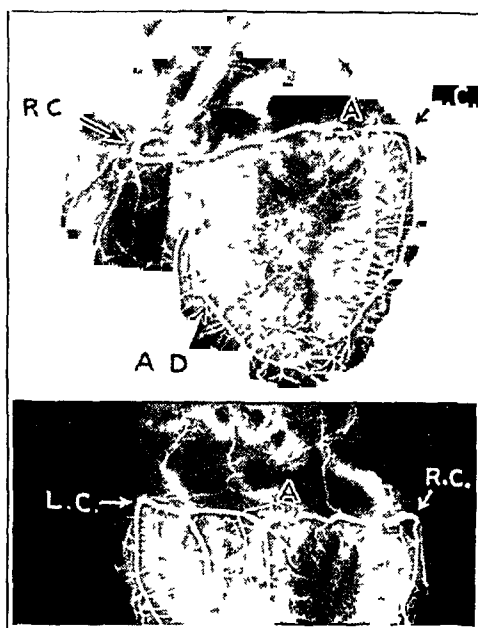


Fig 7—A heart after injection of the right coronary artery only. Previously there had been produced chronic complete occlusion of the circumflex branch of the left coronary artery and ligation of the anterior descending branch. No gross myocardial scar was present. An unusually large anastomotic branch at the crux of the heart is evident. *RC*, indicates the right coronary artery, *LC*, the circumflex branch of the left coronary artery, *AD*, the anterior descending branch, and *A*, anastomosis.



Fig 8—Region of the crux of 3 hearts, 2 of which have been subjected to chronic occlusion of the circumflex branch of the left coronary artery and 1 of which has recovered from ligation of the same vessel. The arrows indicate the small anastomoses that usually occur in this region.

communications and the occasional presence of a large anastomotic vessel at the crux, it is more difficult to demonstrate anastomoses by barium mixtures, but enlarged vessels passing to the right coronary artery from the anterior descending branch are readily seen after injections of india ink

As the anastomotic channels are placed in regions which can readily be shown to contain small communicating branches in the normal heart, it is evident that the connections develop from preexisting vessels. Apparently, the main site of these connections depends on the vagaries in the development of the coronary vessels, and the communications which are congenitally the largest will far outstrip other potential communicating vessels in the supply of a collateral circulation. Thus, while



Fig 9—A heart after acute ligation of the septal branch (middle arrow), chronic occlusion of the right coronary artery (left arrow), ligation preceded by constriction of the anterior descending branch of the left coronary artery (right arrow) and ligation of the posterior descending branch of the left coronary artery. No macroscopic scar was observed in the heart. Note the tortuous septal anastomoses.

in most instances the largest anastomotic vessels are found over the apex of the left ventricle (fig 4 *B*), in some instances a large anastomotic channel may be present on the auricles (fig 3 *B*), or more rarely at the crux of the heart (fig 7) or in the substance of the septum (fig 9).

That the hearts in which the three main branches were occluded were nourished through the main coronary stems is indicated by the complete injection of the coronary tree through the coronary ostia (figs 5 and 6) and is substantiated by the fact that the heart functioned normally in a heart-lung experiment.

EFFICACY OF TISSUE GRAFTS AS A NEW SOURCE OF BLOOD SUPPLY TO
THE HEART

Since, as has been shown, the main coronary vessels could be severely constricted or occluded experimentally without disturbance of the cardiac function, it was necessary to set up different criteria of the efficacy of tissue grafts as blood carriers

The following questions were subjected to scrutiny

- 1 Would the presence of pericardial adhesions or tissue grafts on the heart with intact coronary arteries prevent or mitigate the severity of myocardial infarction after coronary ligation?
- 2 Would the injection of tissue grafts and histologic study of the adhesions support the view that these were adequate to carry any considerable volume of blood?
- 3 In a condition in which the coronary arteries were chronically occluded, would it be possible to demonstrate increasingly large collaterals through the graft?
- 4 If a graft had been in place on the heart during chronic occlusion of the main coronary arteries, would there be any disturbance of myocardial function after severing the stem of the graft?
- 5 Under the same conditions as those mentioned in 4, could there be demonstrated any blood flow through the graft?
- 6 Was there any evidence that the massive pericardial adhesions which were produced exerted any unfavorable effect on the function of the heart?
- 7 Could the experimental results be used in support of or against clinical surgical applications?

The foregoing questions were answered as follows

- 1 It could not be demonstrated that pedicled grafts of pectoralis or latissimus dorsi muscle or of omentum had any beneficial effect in the prevention of infarction after ligation of the normally patent anterior descending artery when such grafts had been in place for from three weeks to nine months. One dog died on the operating table after ligation of this branch, 1 died suddenly twelve hours after the operation, 1 died of heart failure on the eighteenth day after operation, and 2 others which survived showed scars involving nearly the whole thickness of the ventricular wall (fig 10). Small amounts of india ink could be shown to pass into the tissue of the graft when injected into the coronary arteries, but no barium mixture passed through the communications
- 2 and 3 In most instances the thin layer between the myocardium and the muscle graft was observed to contain vessels on histologic examination. While the previous presence of coronary constriction seemed to favor the injection of an increased amount of india ink

across the graft, this was not necessarily true. When thick sections of the myocardium and graft were dehydrated and cleared, the thin intervening layer appeared clear and avascular, even when both the heart and the graft were heavily loaded with india ink. In 2 hearts the graft was well injected with a suspension of barium sulfate

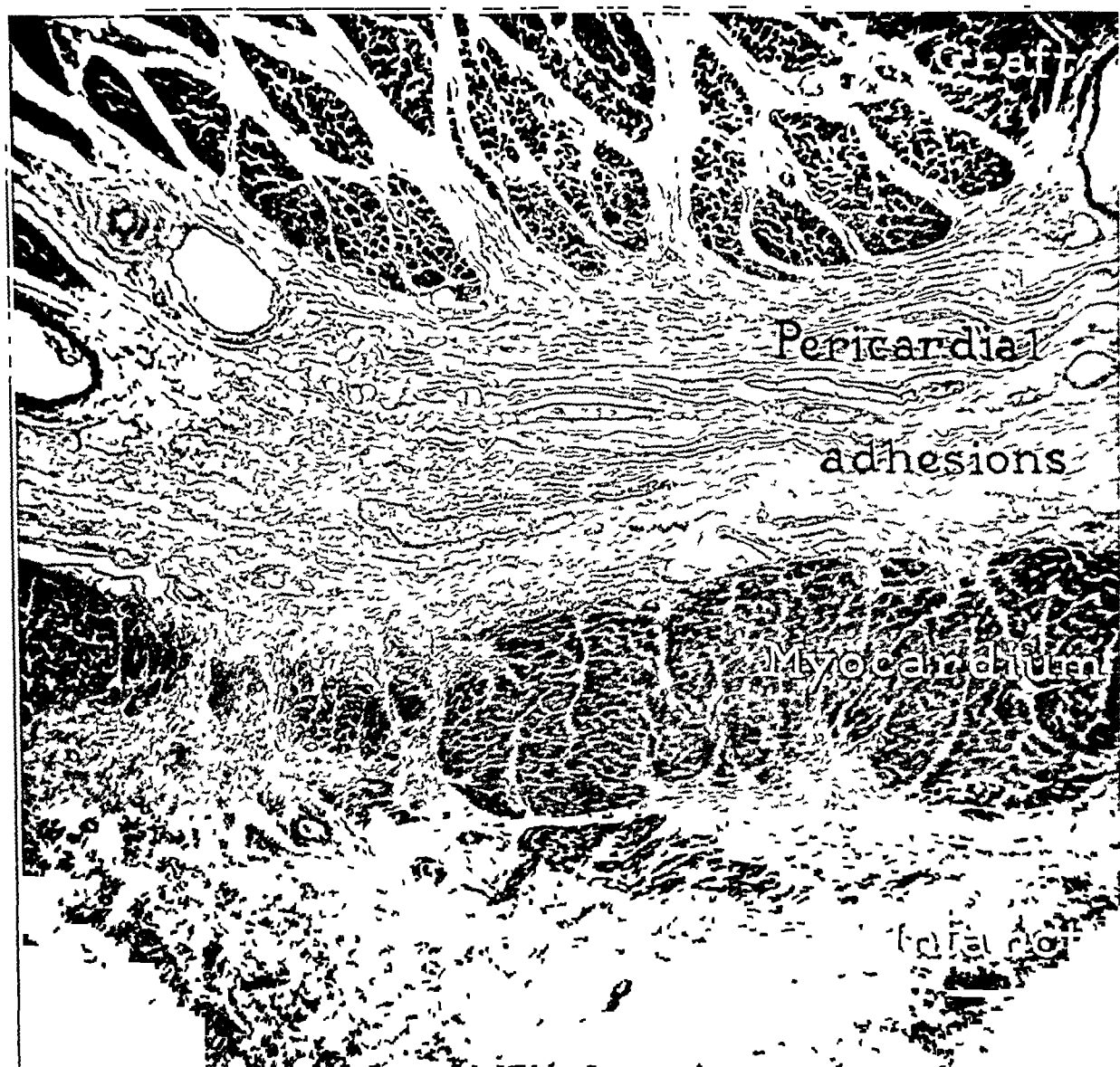


Fig 10—Infarct in the myocardium and vessels in the pericardial adhesions and in the muscle graft. The dog died on the eighteenth day after ligation of the anterior descending branch of the left coronary artery. The muscle graft had been applied ten months previously.

through the injection of the coronary vessels, but the communications through the region of the scar were not macroscopically distinct in the cleared specimens.

It was found that omental grafts formed adhesions to the heart that were readily separable, and that if no injury was done to the epicardium, adhesions were often completely absent. When adhesions were present and injections of india ink were made into the omentum, small vessels entering the heart and filling the coronary arteries were sometimes seen. These small vessels, which were few, were readily observed in cleared specimens. No increase in vascularization was seen after progressive coronary occlusion, and in only 1 instance did a small amount of the suspension of barium sulfate enter any of the coronary arteries when this material was injected into the omental graft.

- 4 In 3 dogs with muscle grafts and in 3 with omental grafts on their hearts, in which occlusion of the three main coronary vessels had been produced, the grafts were cut extrathoracically. Except for 1 dog that died of operative pneumothorax, recognized too late for resuscitation, the animals were in no way inconvenienced by section of the graft, their tolerance to work on the inclined treadmill was unchanged, and there were no electrocardiographic changes to indicate loss of blood supply to the myocardium.
- 5 No significant volume of blood could be demonstrated to flow through the pericardial adhesions. When a heart-lung preparation was made with the organs in situ, and the thoracic and abdominal parts of the aorta were separately perfused with a 30 per cent mixture of blood in Ringer's solution and colored with blue azo dye, small amounts of the dye might appear in the blood expelled by the heart. By comparing the color of the supernatant fluid of a centrifuged specimen of the blood ejected by the heart, before any recirculation has occurred, with that of serial dilutions of the perfusate entering the systemic arteries, the amount of fluid entering the heart through the extracardiac anastomoses may be estimated. In all the heart-lung experiments the perfusing pressure into the grafts was kept at values between 110 and 130 mm of mercury, while the peripheral resistance in the heart-lung circuit was varied from 60 to 80 mm.

In preparations in 3 normal animals, dye was recognized in the cardiac output in 2 animals, and quantitatively amounted to a flow of from 0.5 to 2 cc per minute. In 1 animal with a muscle graft and intact coronary vessels, the flow amounted to from 2 to 3 cc per minute, and in 1 animal with an omental graft and intact coronary vessels it amounted to from 2 to 4 cc per minute. By this method it could not be shown that there was any increase in flow through the adhesions in cases of constriction or occlusion of the coronary arteries.

In 2 preparations in which the three main branches of the coronary arteries were occluded, no dye at all could be recognized in the cardiac

output The grafts had been in place and the coronary arteries had been progressively occluded over periods of from nine to twenty months

- 6 The pericardial adhesions that were produced seemed to exert no harmful effect on the heart Hypertrophy was seen in only 1 animal This animal, after having had seven intrathoracic operations, appeared perfectly well, but when it was finally killed, the right ventricular wall was observed to be definitely thickened, measuring 0.6 to 1 cm In 3 instances, dogs died with congestive heart failure within two weeks after operation when muscle grafts had been extensively stitched to the right ventricle If, however, grafts were loosely applied to this ventricle, firm adhesions developed, and the operation was withstood as well as operations on the left ventricle Records of blood pressure obtained by the Hamilton technic, with simultaneous respiratory tracings, showed no pulsus paradoxus, the venous pressures were normal, and tolerance to exercise was normal in animals later shown to have extensive adhesions between the heart and the wall of the chest
- 7 It is difficult to make clinical application of conclusions drawn from animal experiments to a surgical operation designed to produce a blood supply to the heart From the experiments in the present work, it seems that the heart of the healthy dog possesses a mechanism of collateral blood supply of great individual variability but of extreme competence if it is allowed to develop by reason of constriction or slow occlusion of major coronary vessels The results reported do not necessarily vitiate the clinical applicability of this type of operation on the heart, but cause grave doubt concerning its experimental basis It is believed that if many more experiments had been performed the possibility of enlargement of vessels in pericardial adhesions might have become a reality, but it is doubted whether any experiment could be devised in which the heart could be made to beat as a result of perfusion of pericardial adhesions

COMMENT

It may be noted that in many ways the results of the operations on the present series of dogs are similar to those of Beck and Tichy²¹ The main difference lies in the interpretation of the results, with the additional demonstration that hearts with the three main vessels occluded functioned well when supplied with blood through the coronary ostiums in heart-lung preparations The behavior of healthy coronary arteries is not unlike that of the systemic arteries in that occlusion in any one region is readily bridged, if the occlusion does not occur too rapidly

These statements are in accord with those of Mautz and Gregg⁴³ and of Mautz and Beck,²² who observed large collaterals to chronically occluded vessels, and with the results of Blum, Schauer and Calef,⁴⁴ who found that in chronic occlusion of the anterior descending artery of the dog no infarction occurred in many instances. It is believed that the last-named authors did not pay enough attention to the possibility that when infarction was present acute occlusion due to twisting of the clamp might have occurred.

It is believed that the experiments of Mann, Herrick, Essex and Baldes²⁷ on the maintenance of blood flow through constricted vessels explain why the hearts of many of the animals were not inconvenienced by constricting collars on the coronary vessels.

The sudden death of the animals with constricted coronary vessels, within a week of operation, has been thought to be due to ventricular fibrillation and to be analogous to the sudden death of some patients with coronary disease in whom an acute lesion is not observed on post-mortem examination.

The evident complete reestablishment of cardiac function after the healing of infarction in the experimental animal has not been stressed since the time of Hirsch and Spalteholz.⁸

Knowledge of experimental occlusion of coronary vessels has progressed from the time when ligation of the vessels was found to be lethal, through stages of production of infarction and of recognition that the infarct was smaller than the region supplied by the ligated vessel, to the present, when it has been demonstrated that if occlusion occurs slowly myocardial injury may not result.

As a rule, the dogs in the present series were not exercised during the first week after acute occlusion of their coronary vessels. This is to be noted, as Sutton and Davis⁴⁵ have shown in studies of experimental myocardial infarction that if the animal is permitted to rest for a week after operation small firm scars without thinning of the ventricular wall result, while if the animal is exercised a thin bulging scar is seen.

In cases of injuries to the human heart, such as stab and bullet wounds, it has sometimes been necessary to ligate large coronary arteries. It is of considerable interest that in these human hearts, in which a coronary artery had been ligated, if recovery from acute infarc-

43 Mautz, F. R., and Gregg, D. E. Dynamics of Collateral Circulation Following Chronic Occlusion of the Coronary Arteries, *Proc Soc Exper Biol & Med* **36** 797-801 (June) 1937.

44 Blum, L., Schauer, G., and Calef, B. Gradual Occlusion of a Coronary Artery. An Experimental Study, *Am Heart J* **16** 159-164 (Aug) 1938.

45 Sutton, D. C., and Davis, M. D. Effects of Exercise on Experimental Myocardial Infarction, *Arch Int Med* **48** 1118-1125 (Dec) 1931.

tion occurred, restitution of function was often complete. For a review of these cases of cardiac injury with operative treatment, the report of Gronwald⁴⁶ is particularly instructive.

Concerning the innocuous effect of pericardial adhesions, the present study confirms that of Hosler and Williams⁴⁷. It was not possible to study the ratio of heart weight to body weight except in a few instances, as the heart and the tissues adherent to it were injected and fixed before study. Heilmann and Musser⁴⁸ have reported that adhesions resulted in an increase in this ratio, particularly if mediastinitis had been produced as well.

Observations that the uninjured epicardium may not form any adhesions to tissues placed on it are in agreement with those of Klose,⁴⁹ who found that he could replace portions of the parietal pericardium with fat without the formation of adhesions.

As previous investigators have pointed out, standardization of experiments dealing with repeated operations to occlude the coronary vessels is impossible, owing to anatomic variability in the arteries and unavoidable variations in the operative procedures. In some instances, in which the heart had been subjected to several previous operations, identification of vessels was difficult, and occasionally, when sutures were used to tie off regions in which a vessel was thought to lie, injection at a later date showed the vessel to be still patent. All the dogs were operated on under anesthesia induced with ether or intravenous injection of pentobarbital sodium (nembutal), and surgical technic was used throughout. The chest was usually entered through an intercostal incision.

As has been mentioned in several places, the tolerance of the animals to exercise was tested on an inclined treadmill run by an electric motor at a constant rate. The animal, previously trained to run on the treadmill, was allowed to run from twenty to thirty minutes at 3 miles (1.6 kilometers) per hour on a slope of 25 degrees to the horizontal. While this may not be severe exercise, it has been believed to indicate good cardiac function and stamina. For 3 dogs with the three main coronary branches occluded, the test was altered by increasing the rate to 4.5 miles (7.24 kilometers) an hour and by decreasing the time to fifteen minutes, and these dogs behaved similarly to the normal kennel dogs. Two of

46 Gronwald, G. Ueber Spätfolgen nach Herzmuskel- und Coronargefäßverletzungen, *Arch f klin Chir* **174** 249-280, 1933.

47 Hosler, R. M., and Williams, J. E. A Study of Cardiopericardial Adhesions, *J Thoracic Surg* **5** 629-640 (Aug.) 1936.

48 Hermann, G., and Musser, J. H. Experimental Pericarditis, *Am Heart J* **4** 268-279 (Feb.) 1929.

49 Klose, H. Die reine Synechie, und der plastische Ersatz des Herzbeutels I Chirurgisch-experimenteller Teil, *Arch f klin Chir* **117** 138-148, 1921.

these animals received 1 cc of pitressin intramuscularly ten minutes previous to the test, without any apparent decrease in their tolerance to the standard test as outlined in this paragraph

SUMMARY

The anatomy of the coronary arteries in the dog is reviewed, with emphasis on the presence of a large septal branch and the free anastomoses between the ventricular and the auricular coronary branches. Extracardiac communications on the great vessels at the base of the heart have been demonstrated without difficulty.

Constriction of the main coronary vessels to an estimated 35 to 60 per cent of their diameter over lengths of 7 mm caused no disability if the animals recovered from the immediate effects of the operations. Ligation of severely constricted vessels could frequently be made without the production of infarction. Complete occlusion without the production of infarction has been accomplished by constricting metal collars which were loosely anchored to the wall of the chest.

By these methods it has been possible to occlude the three main coronary branches in the dog without the production of infarction or demonstrable cardiac disability. Reestablishment of the circulation has occurred from the first branches of the coronary stems and by enlargement of preexisting collateral channels.

So far as these studies on coronary occlusion in dogs are concerned, the role played by vascular channels in pericardial adhesions in supplying blood to the myocardium has been minimal or nonexistent. The possibility that the small vascular connections between a graft and the heart might develop to a functioning value cannot be denied, but in the experiments seemingly favorable to such a result it has not occurred.

MECHANISM OF DIGITALIS ACTION IN ABOLISHING HEART FAILURE

HARRY GOLD, M D
AND
McKEEN CATTELL, M D
NEW YORK

In a paper which we published recently,¹ we showed that digitalis exerts a direct action on the systolic force of mammalian cardiac muscle. Our preparation was the papillary muscle of the cat's right ventricle immersed in Ringer's solution. We measured tension with the isometric lever and recorded it photographically. Since the muscle was driven at a fixed rate, since there was no coronary circulation or systemic circulation and since the drug reversed the direction of failing systolic tension while the initial (diastolic) tension was maintained constant, we concluded that the digitalis glucosides increase the force of contraction of failing mammalian cardiac muscle by direct action on the muscle. This effect applies to all the digitalis glucosides which have been used: ouabain, digitoxin (Merck), digitalin (Nativelle) and digitanin C (Sandoz). Figure 1, reproduced from that paper, shows the essentials of the results.

Since then we have explored the matter further. We have tested the effect of digitalis glucosides not only at optimum initial tension, but also at low and at excessive initial tensions. The muscle was made to work in blood and serum as well as in Ringer's solution. We also recorded changes in initial tension as an expression of "tone" during the action of the glucosides.

We found that the marked increase in the systolic force of contraction which was originally obtained in Ringer's solution also occurs when the muscle is immersed in blood and serum, that a similar effect is obtained when the muscle is operating at optimum initial tension and when it is inadequately stretched or overstretched, and that the direct

From the Department of Pharmacology of Cornell University Medical College

A preliminary account of this work was presented at the International Physiological Congress in Zurich, Aug 18, 1938 (Kongressbericht II des XVI internationalen Physiologenkongresses, Zurich, 1938, p 183)

1 Cattell, McK, and Gold, H. The Influence of Digitalis Glucosides on the Force of Contraction of Mammalian Cardiac Muscle, *J Pharmacol & Exper Therap* **62** 116, 1938

action of the glucosides was one on systolic force and not on tone, for tone considered as initial tension did not change when the systolic force was mounting

Figure 2 illustrates the effect of one of the glucosides on the muscle in blood at optimum and at excessive initial tension. Figure 3 shows the effect of the glucoside simultaneously on the tone and on the

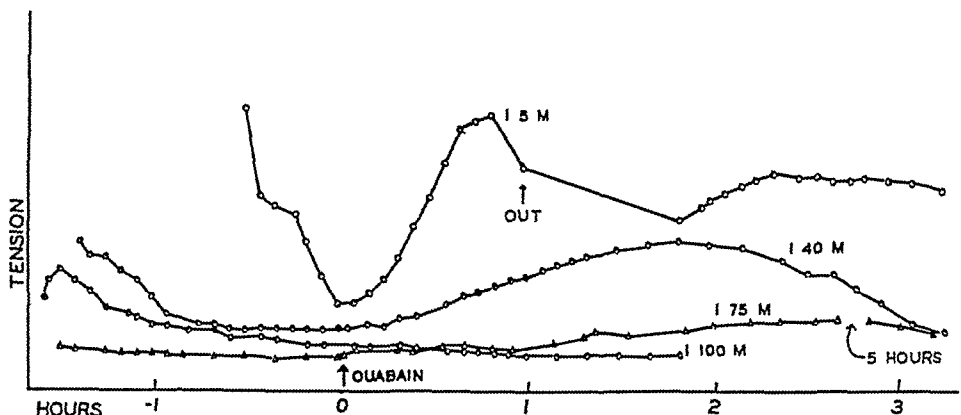


Fig 1—Effect of different concentrations of digitalis glucosides on systolic tension in the papillary muscle of the cat

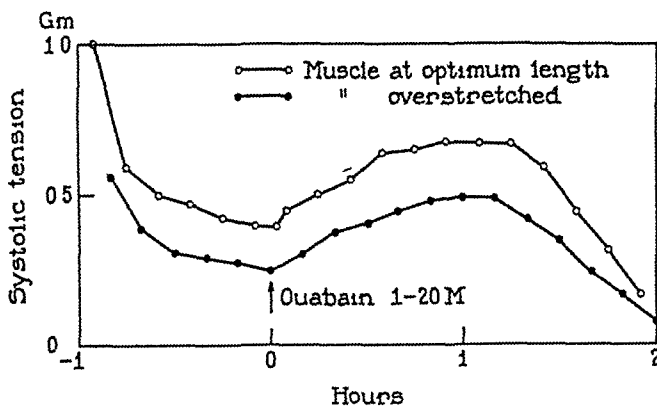


Fig 2—Effect of digitalis glucoside on papillary muscle contracting under optimum and under excessive diastolic tension. Papillary muscle of a cat in a chamber containing the cat's defibrinated blood was used. The weight of the muscle was 50 mg, and its resting length, 10 mm. At optimum stretch diastolic tension equaled 17 Gm and systolic tension, 1.0 Gm. When the muscle was overstretched diastolic tension equaled 4.5 Gm and systolic tension, 0.55 Gm. Records were taken at the two diastolic tensions alternately at five minute intervals, the shift to the new diastolic tension being made immediately after each tracing in order to allow about five minutes for attaining equilibrium at each tension before a record was made.

systolic force of the muscle in blood serum. The marked increase in systolic force is not attended by any changes in tone. Figure 4 shows the type of records obtained in the experiments with the papillary muscle.

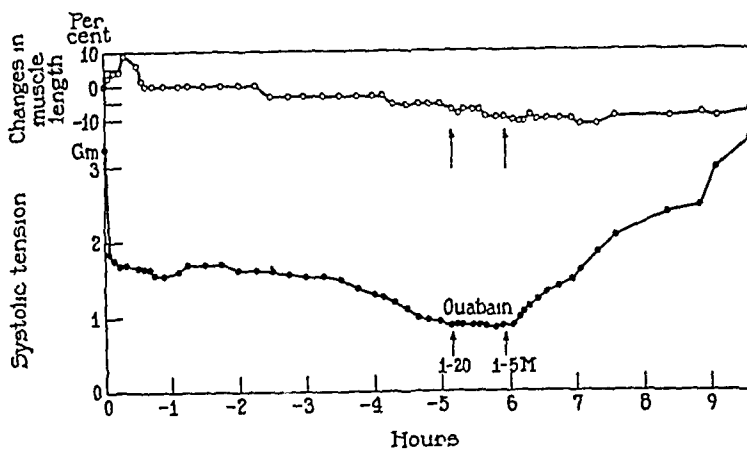


Fig 3—Effect of digitalis glucoside on “tone” and systolic tension The preparation consisted of a papillary muscle from the right ventricle of a cat in a chamber containing the cat’s serum Resting length of the muscle, was 115 mm, and its weight was 20 mg The diastolic tension was 12 Gm All the records of systolic tension were made at the constant diastolic tension of 12 Gm Tendency of the muscle to increase or decrease its diastolic tension was counteracted by allowing the muscle to lengthen or shorten as indicated in order to maintain a constant diastolic tension These adjustments of the muscle length reveal, therefore, the tendency of the muscle to change its “tone” (diastolic tension) throughout the experiment (upper line) Note that the muscle was capable of undergoing changes in diastolic tension (tone) but failed to show any such changes during the action of the glucoside on systolic tension

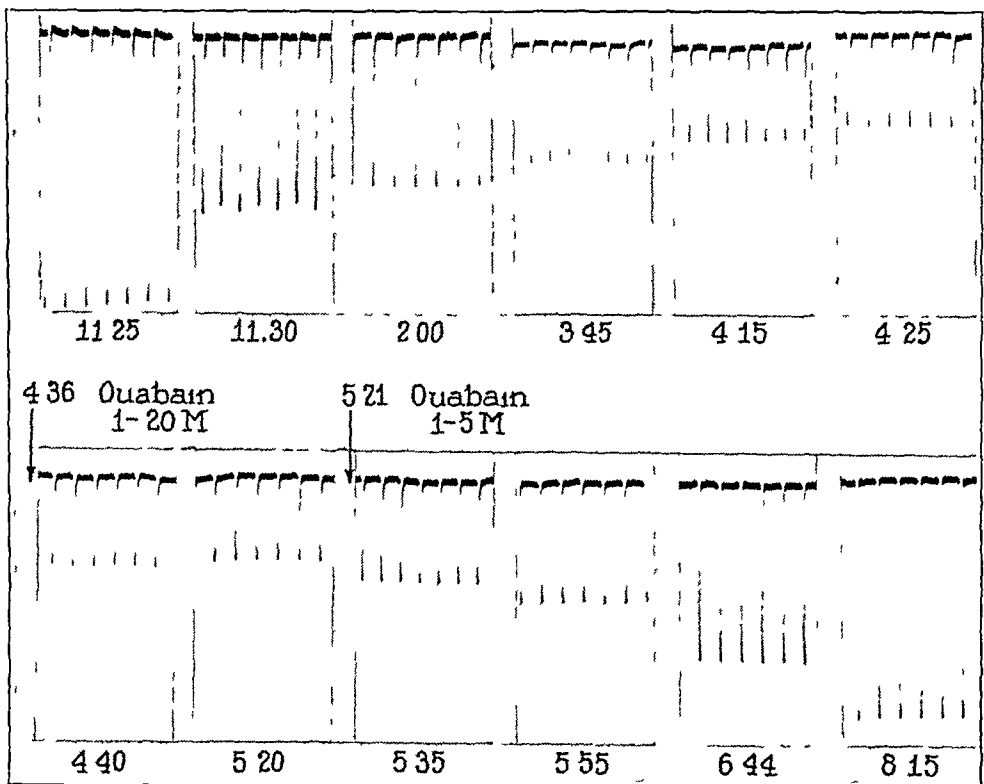


Fig 4—Selected tracings from the experiment charted in figure 3, showing the type of record obtained in the experiments on papillary muscle

A more detailed analysis of the action on muscle is provided by a number of workers. Cattell² showed that under the action of digitalis striated muscle loses potassium, so that the effect may result from a disturbance of mineral metabolism with relative increase of calcium. This hypothesis receives support from the subsequent finding by Wood and Moe³ of an increase of plasma potassium after therapeutic and toxic doses of digitalis glucoside in heart-lung preparations and from the report of Calhoun and Harrison,⁴ who found that the cardiac muscle of dogs loses potassium after large doses of digitalis. Wedd⁵ expressed the opinion that the release of potassium is a toxic phenomenon. Peters and Visscher⁶ showed that under the action of digitalis heart muscle not only increases its total output of energy but utilizes energy more efficiently, converting a relatively greater amount into external work.

Since all the effects we observed occurred with concentration of the drug well within the range of doses used in therapeutics, we consider it justifiable to make an application of the results of the studies on papillary muscle. We present the view that digitalis abolishes clinical heart failure by primary action on the heart muscle to increase the systolic force.

That digitalis increases the contractility of the heart is generally known. Cohn and Stewart⁷ demonstrated it in the dog by means of the moving film. Starr and his collaborators⁸ found that in man the constant effect of digitalis was to increase the ratio of work per beat to the size of the heart. On the basis of the change in this ratio they defined stimulation of the heart and their results showed that the drug produces the same effect on normal hearts as on those in failure. However, the evidence for a primary action on systolic force was not con-

2 Cattell, McK. The Influence of Ouabain on the Contraction of Striated Muscle, *J Pharmacol & Exper Therap* **62** 459, 1938

3 Wood, E H, and Moe, G K. Studies on the Effect of the Digitalis Glucosides on Potassium Loss from the Heart of the Heart Lung Preparation, *Am J Physiol* **123** 219, 1938

4 Calhoun, J A, and Harrison, T R. Studies on Congestive Heart Failure IX. The Effect of Digitalis on the Potassium Content of the Cardiac Muscle of Dogs, *J Clin Investigation* **10** 139, 1931

5 Wedd, A M. The Influence of Digoxin on the Potassium Content of Heart Muscle, *J Pharmacol & Exper Therap* **65** 268, 1939

6 Peters, H C, and Visscher, M B. The Energy Metabolism of the Heart in Failure and the Influence of Drugs upon It, *Am Heart J* **11** 273, 1936

7 Cohn, A E, and Stewart, H J. The Relation Between Cardiac Size and Output Per Minute Following the Administration of Digitalis in Normal Dogs, *J Clin Investigation* **6** 53, 1928

8 Starr, I, Gamble, C J, Margolies, A, Donal, J S, Jr, Joseph, N, and Eagle, E. A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size, on Respiration, on Metabolic Rate and on the Electrocardiogram, *J Clin. Investigation* **16** 799, 1937

clusive, because the experiments bearing on this matter were susceptible of alternative explanations. So little conviction did they carry that at present the most popular formulations as to how digitalis abolishes clinical heart failure take little cognizance of a primary action on systolic force and explain the increased force of the heart beat as the indirect result of other effects of digitalis, namely (1) primary slowing of the rate, (2) primary action of increasing cardiac tone, that is, shortening the muscle so as to bring it to a more favorable length, (3) pooling of blood in the liver by primary constriction of the hepatic veins, thus lowering the venous pressure and relieving the overdistended heart, and (4) reducing the size of the heart that is overdilated to facilitate coronary flow.

We may now proceed to consider the evidence bearing on the "rate" hypothesis, the "tone" hypothesis and the "liver" hypothesis of digitalis action.

"RATE" HYPOTHESIS OF DIGITALIS ACTION

Digitalis produces its most dramatic effects on the symptoms and signs of heart failure in patients with auricular fibrillation in whom pronounced ventricular slowing occurs. This has given rise to the view that slowing is the primary effect of the drug (depression of auriculo-ventricular conduction) and the cause of the improved cardiac function. Lewis (1919)⁹ attributed the therapeutic effects solely to slowing. The thoroughly controlled studies by Luten (1924)¹⁰ and Marvin (1927)¹¹ on groups of patients with regular sinus rhythm and heart failure with edema (especially in arteriosclerotic cardiac disorders) showed beyond reasonable doubt, however, that cardiac slowing is not essential to the therapeutic effect of digitalis. While in some of those cases in which the rate was rapid during the failure slowing took place simultaneously with improvement, in many others the rate was normal during the stage of failure and remained unchanged even during dramatic relief of the symptoms and signs of heart failure.

In the normal animal the heart rate may speed up as high as 200 a minute before the circulation begins to suffer (Wiggers, 1931¹²). The critical level, however, is probably shifted by many factors, such

9 Lewis, T. On Cardinal Principles in Cardiologial Practice, *Brit M J* 2 621, 1919.

10 Luten, D. Clinical Studies of Digitalis. I. Effects Produced by the Administration of Massive Dosage to Patients with Normal Mechanism, *Arch Int Med* 33 251 (Feb) 1924.

11 Marvin, H. M. Digitalis and Diuretics in Heart Failure with Regular Rhythm, with Especial Reference to Importance of Etiologic Classification of Heart Disease, *J Clin Investigation* 3:521, 1927.

12 Wiggers, C. J. Physiologic Meaning of Common Clinical Signs and Symptoms in Cardiovascular Disease, *J A M A* 96 603 (Feb 21) 1931.

as the capacity of the muscle, possibly the character of the rhythm¹³ and the coronary blood supply. There is no way at present of determining what rate is excessive in various conditions, but the view prevails that heart rates appreciably above normal are injurious to cardiac contraction.

We may present, therefore, some of the evidence against the *a priori* assumption that slowing the ventricular rate will improve the cardiac function and abolish signs of heart failure.

1 In the experiments with the papillary muscle we observed that increasing the rate of stimulation usually did not diminish but rather increased the force of the contraction, whether the rhythm was regular

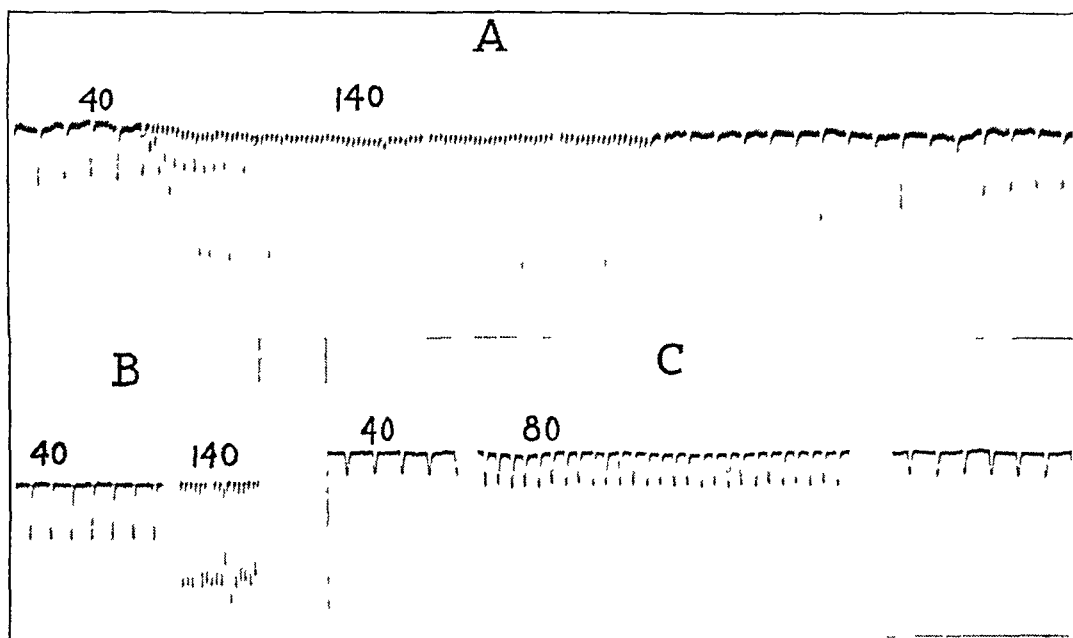


Fig 5—Effect of rate on tension in papillary muscle. In experiments *B* and *C* the acceleration took place spontaneously, in *A* it was induced by speeding up the electric stimulation.

or irregular. This applied over a wide range of rates, from 50 to as high as 200 a minute. Figure 5 illustrates such experiments. Similar observations have been made independently by Kikuta¹⁴ (1937).

2 It is well known that one physiologic response to physical stress is cardiac acceleration. When the stress is over the rate slows. The

13 Stewart, H. J., and Cohn, A. E. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. II. The Effect on the Output of the Hearts of Dogs Subject to Artificial Auricular Fibrillation, *J. Clin. Investigation* **11** 897, 1932.

14 Kruta, V. Sur l'activité rythmique du muscle cardiaque. I. Variations de la réponse mécanique en fonction du rythme, *Arch. internat. de physiol.* **45** 332, 1937.

heart rate of the average untreated patient with auricular fibrillation and heart failure is of the order of 130 or 140 a minute. If the rapid rate were embarrassing the heart and circulation, it is strange that the heart would not beat more slowly, since the ventricle in most cases of auricular fibrillation obeys the same laws which regulate the normal sinus rhythm, atropine accelerates the rate, the heart beats faster during effort, it slows during rest, and it is subject to physiologic vagal control. It seems justifiable to assume, therefore, that this rapid rate is, in many cases at least, a favorable adaptation to demands rather than the cause of failure.

3 The very close association between weakness of the heart and cardiac slowing after ordinary therapeutic doses of digitalis and the resistance to slowing when the heart is not damaged strongly suggest that slowing by digitalis is in most cases secondary to primary improvement of the heart function. This point of view has been recently developed in interesting contributions by Luten¹⁵ and by Luten and Jeffreys¹⁶. Additional evidence indicating that the vagal phase of slowing by digitalis in cases of auricular fibrillation is secondary to improved function is presented in a study by Gold, Kwit, Otto and Fox¹⁷.

These lines of evidence leave scant support for the view that cardiac slowing is a primary action by which digitalis abolishes heart failure in the average patient with sinus rhythm or with auricular fibrillation.

CARDIAC OVERDISTENTION AS A CAUSE OF FAILURE

In heart failure blood tends to accumulate on the venous side of the pulmonary or the systemic circuit, depending on whether the failure is predominantly of the right or of the left ventricle. The resulting increase in the diastolic pressure in the ventricles stretches the muscle fibers, which, in accordance with Starling's "law of the heart,"¹⁸ increase their energy output as they grow longer. The lengthening of the muscle fibers (enlargement of the heart) with the increase in the venous pressure must therefore be viewed as an adaptive mechanism by which the weakened heart muscle may boost its output of energy to meet the demands of the circulation. Heart muscle may be lengthened to a

15 Luten, D. The Relationship of Tachycardia to Cardiac Insufficiency, *Am Heart J* **12** 435, 1936.

16 Luten, D., and Jeffreys, E. O. The Clinical Significance of Auricular Fibrillation, *J A M A* **107** 2099 (Dec 26) 1936.

17 Gold, H., Kwit, N. T., Otto, H., and Fox, T. Physiological Adaptations in Cardiac Slowing by Digitalis and Their Bearing on Problems of Digitalization in Patients with Auricular Fibrillation, *J Pharmacol & Exper Therap* **67** 224, 1939.

18 Starling, E. H. The Linnacre Lecture on the Law of the Heart, Given at Cambridge, 1915, London, Longmans, Green & Co., 1918.

critical point, however, beyond which further stretching tends to diminish the force of contraction. The belief prevails that in clinical heart failure dilatation may have proceeded to such an unfavorable degree as to embarrass the force of the heart's contraction. From this the notion arises that the function of the heart will be improved if the diastolic length is shortened so that the heart is no longer overstretched.

The "liver" hypothesis and the "tone" hypothesis of digitalis action have one point in common, namely, both involve the assumption that in heart failure the cardiac muscle is overdistended, that the fiber has been stretched beyond the critical point and that if its diastolic length can be shortened its systolic force will increase. One of the views assumes that the shortening is brought about by direct action of digitalis on the diastolic size of the heart. The other assumes that the diastolic size of the heart becomes less because the venous pressure is lowered by pooling the blood in the liver.

The first objection to these hypotheses is that there is no reason for supposing that the heart muscle is overstretched (overdilated chambers) in ordinary cases of heart failure. What is the pressure that will overstretch the heart muscle? The only pressure is the venous pressure, and its magnitude is not sufficient to cause overstretching of ventricular muscle.

In experiments with the isolated papillary muscle we observed the well known phenomenon that as the length of the muscle is increased within a certain range the systolic tension rises and as the muscle is shortened the systolic tension falls. It is extremely difficult to overstretch heart muscle. In our experiments with the papillary muscle as well as with strips of the right ventricle we observed that these muscles must be stretched by a force equal to or exceeding the systolic tension before they become overstretched, i. e., before the systolic tension begins to fall. Forces of that magnitude are not encountered in heart failure. Venous pressure in clinical heart failure is rarely as high as 15 cm. of water, and even such high venous pressure is only about 25 per cent of the systolic pressure in the right ventricle. Experimentally, therefore, heart muscle is not in an overstretched state when there prevail such high ratios of systolic to diastolic tension as occur in the average case of heart failure.

The critical venous pressure in the dog has been placed between about 25 and 30 cm. of saline solution by Wiggers and Katz¹⁹. Up to this level as the venous pressure was raised the cardiac discharge increased, but beyond it the heart began to fail and the discharge diminished.

19 Wiggers, C. J., and Katz, L. N. The Contour of the Ventricular Volume Curves Under Different Conditions, *Am J Physiol* 58:439, 1922.

We performed a series of 4 experiments on cats in the hope of throwing further light on the effect of high venous pressures on the systolic force of the ventricle and the influence of raising and lowering the venous pressure during acute heart failure under these conditions. The cats were anesthetized with a solution of diallylbarbituric acid with ethyl carbamate (solution dial-ciba with urethane). Diastolic and systolic tensions in the left ventricle were recorded optically by a Wiggers modification of the Frank optical manometer. A cannula was inserted into the left auricle and connected to a reservoir by means of which venous pressure could be raised or lowered. Changes in pressure were recorded after complete occlusion of the ascending aorta close to the heart. Typical results are shown in figure 6. A rise of diastolic tension was always associated with increased force of the heart (increased systolic tension). In figure 6 *B* the ventricle became stronger even with such rises in diastolic tension as from 46.8 to 76 mm. of mercury, the latter corresponding to a venous pressure of 98.7 cm. of water. This diastolic tension was approximately one third of the systolic tension in the left ventricle. When the heart began to fail as the result of overwork and impaired circulation the systolic and diastolic pressures fell. The failing heart, however, obeyed the same law as it had in the normal state. With lowering of the venous pressure the force of contraction declined, and with raising of the venous pressure the force increased. Considering the failing heart as "overstretched" in that state in which a reduction of the stretch increases its force of contraction, one notes that even under these extreme conditions of failure and high venous pressure the heart did not behave like an overstretched muscle.

How some of these matters stand in man cannot be stated with certainty. The importance of elevated venous pressure as an adaptive mechanism in clinical heart failure has been emphasized by several workers (Harrison²⁰, McMichael²¹). It has been pointed out by Altschule²² that normally a rise in venous pressure increases the cardiac output but that the high venous pressure in failure is associated with a diminished cardiac output. However, this difference may be only quantitative. McMichael²¹ secured interesting evidence in cases of heart failure in man to the effect that the failing heart does not behave like an overstretched heart and that its output differs only quantitatively from the normal. In normal man a change from the erect to

20 Harrison, T. R. *Failure of the Circulation*, Baltimore, Williams & Wilkins Company, 1935.

21 McMichael, J. The Output of the Heart in Congestive Failure, *Quart. J. Med.* **7** 331, 1938.

22 Altschule, M. D. The Pathology of Chronic Cardiac Decompensation, *Medicine* **17** 75, 1938.

the supine position causes a rise in the venous pressure, which in turn is attended by an increase in the cardiac output. McMichael found that diseased hearts become less susceptible to increments of venous pressure, such rises of venous pressure as occur with postural change produce progressively smaller increases in cardiac output as the heart fails. Even when the failure is fairly advanced and postural changes in venous pressure are ineffectual, however, the larger increase in venous pressure caused by exercise is attended by an increase in the cardiac output. The study by McGuire, Shore, Hauenstein and Goldman²³ also shows that even in patients with congestive heart failure exercise causes an increase in the cardiac output, although this increase is less than occurs in normal persons with similar exercise. The results of these studies in

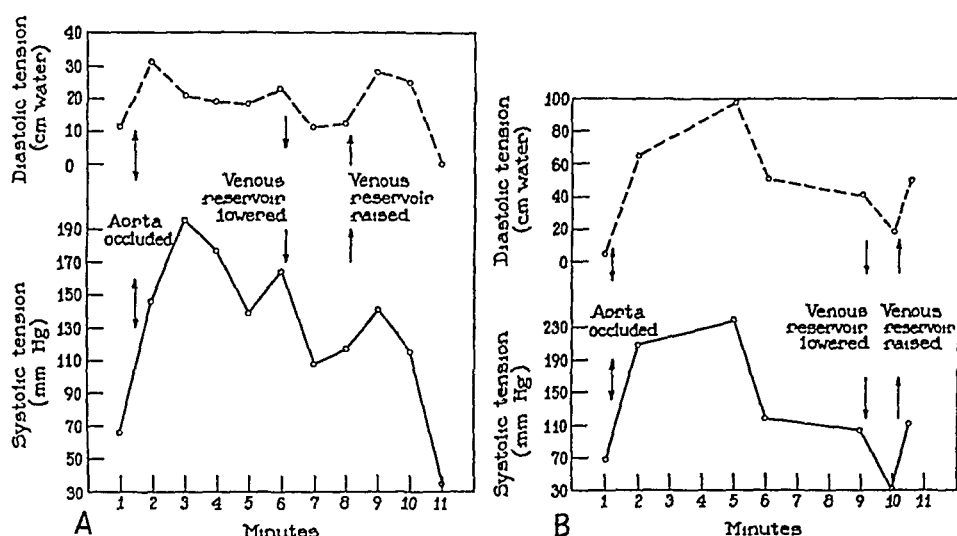


Fig 6—Charts showing the typical effect of venous congestion on the force of contraction of a heart failing as the result of occlusion of the aorta

man are strikingly similar to those obtained in our experiments with the cat's heart shown in figure 6

The view prevails that in heart failure the muscle in its resting period is lacking in fitness for its subsequent systolic contraction. The term "diminished tone (or tonus)" is applied to this lack of fitness, although there is no general agreement as to the physical or physiologic nature of this property. It is commonly considered synonymous with elasticity in the sense of resistance to deformation (Henderson²⁴). If tone of heart muscle is so regarded, one may point out that reduced tone is not necessarily attended by diminished force of contraction (see fig 7)

23 McGuire, J, Shore, R, Hauenstein, V, and Goldman, F. Influence of Exercise on Cardiac Output in Congestive Heart Failure, *Arch Int Med* 63 469 (March) 1939

24 Henderson, Y. Volume Changes of the Heart, *Physiol Rev* 3 165, 1923

In one experiment in which the papillary muscle was stretched 4 mm the force of the systolic contraction (systolic tension) was 10 mm and the resistance to stretch (initial tension) was 91 mm (high tone). When, after further stretching, the muscle was released to the previous length, i. e., 4 mm longer than resting length, the resistance to the maintenance of this length (initial tension) was lower than before, namely, 55 mm (lower tone), but the systolic force was higher (145 mm). Evidence supporting a similar conclusion (favorable influence of lowered tonus) has been reported for the intact dog's heart by Johnson and Katz²⁵. It is therefore not necessarily desirable in the case of the failing heart to attempt by drugs or other means to increase tone in this sense.

The foregoing considerations indicate that clinical heart failure may not involve a state in which the heart muscle is overstretched and

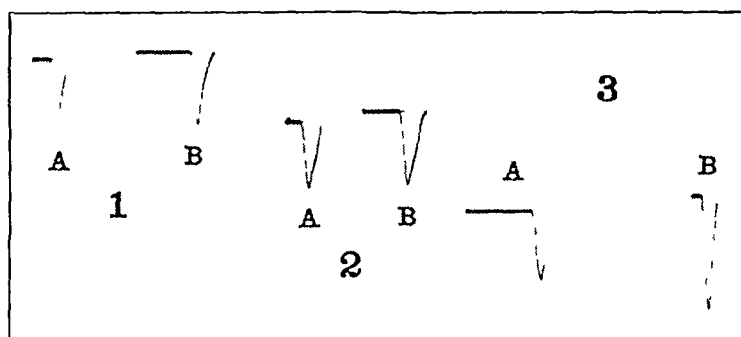


Fig 7—Changes in tension in the strip of the right ventricle of a cat in Ringer's solution and stimulated at intervals at three different lengths (1, 2 and 3). Tracing 1 A was taken immediately after the muscle was stretched to that length, 1 B, five minutes later. Tracings at lengths 2 and 3 were similarly obtained. Note that when equilibrium was reached after the muscle was stretched to a new length, the diastolic tension fell (rise of the base line) and the systolic tension rose.

that the validity of the objective of reducing the diastolic size of the heart as a means of increasing the force of the heart's contraction is open to question.

It is known that reducing venous congestion or return flow to the heart may exert a favorable influence in cases of clinical heart failure although the output may fall,²¹ as seen sometimes in the beneficial therapeutic effects of venesection, of constriction of the veins of the limbs by tourniquet and of the standing posture in cases of acute failure of the left side of the heart. There is no reason for assuming that the beneficial effects are the result of reducing overdistention of the ventricle. They can be brought about in other ways. It is known, for example, that

²⁵ Johnson, V, and Katz, L. N. Tone in the Mammalian Ventricle, *Am J Physiol* 118 25, 1937.

venesection in normal subjects increases the vital capacity,²⁶ a factor that might influence favorably the exchange of gases in heart failure. It may also diminish the viscosity of the blood.²⁷

In perfusion experiments with surviving human hearts, Kountz and Smith²⁸ found that the coronary flow fell off considerably when the heart was dilated as the result of asphyxia. In the case of a large heart with failure it might be argued that the heart is not overdilated and yet is sufficiently dilated to interfere with the coronary circulation. The quantitative aspect of this relationship is the deciding one, but concerning this we have no evidence.

"LIVER" HYPOTHESIS OF DIGITALIS ACTION

Dock and Tainter²⁹ developed the hypothesis that the diminution in the size of the heart and in the cardiac output that occurs in the normal person after the administration of digitalis is due to a direct constrictor action of digitalis on the hepatic veins. This opinion was based on the observations in the dog that under the action of digitalis the portal pressure rises, the liver enlarges, and the venous pressure falls. In their experiments Katz and his associates³⁰ confirmed this phenomenon in the dog, and they concluded that in man digitalis acts not on the heart to abolish heart failure but on the liver to constrict the hepatic veins, exercising its favorable effect by pooling blood in the liver, which in turn reduces the venous congestion and the overdistention of the heart which they believe exist. Whether digitalis causes significant pooling of blood in the liver in man has been fully considered and answered in the negative by Cohn and Steele.³¹ Digitalis does not cause enlargement of the liver or reduce the venous pressure in normal man.³¹

26 Budelmann, G. Ueber den Einfluss des Aderlasses auf die Vitalkapazität der Lunge beim gesunden Menschen, *Klin Wchnschr* **16** 704, 1937.

27 Lewis, T. *Diseases of the Heart*, New York, The Macmillan Company, 1934.

28 Kountz, W. B., and Smith, J. R. The Flow of Blood in the Coronary Arteries in Pathological Hearts, *J Clin Investigation* **17** 147, 1938.

29 (a) Dock, W., and Tainter, M. L. The Circulatory Changes After Full Therapeutic Doses of Digitalis, with a Critical Discussion of Views on Cardiac Output, *J Clin Investigation* **8** 467, 1930. (b) Tainter, M. L., and Dock, W. Further Observations on the Circulatory Actions of Digitalis and Strophanthus, with Special Reference to the Liver, and Comparisons with Histamine and Epinephrine, *ibid* **8** 485, 1930.

30 Katz, L. N., Rodbard, S., Friend, M., and Rottersman, W. The Effect of Digitalis on the Anesthetized Dog. I. Action on the Splanchnic Bed, *J Pharmacol & Exper Therap* **62**:1, 1938.

31 Cohn, A. E., and Steele, M. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. I. The Effect on the Output of the Dog's Heart in Heart-Lung Preparations, *J Clin Investigation* **11** 871, 1932.

In 1909 Schmid³² made some measurements of the portal pressure in the cat after administration of digitalis. The results were variable, and the experiments were not described in sufficient detail to permit analysis. We performed some experiments to test the phenomenon. In each of 4 cats we made simultaneous records of the pressure in the portal vein and in the carotid artery during the administration of ouabain (3 cats) and tincture of digitalis (1 cat). Various anesthetics were used: a mixture of dial, ethyl carbamate and morphine to produce deep narcosis (1 cat), soluble barbitol U S P (sodium barbitol) and morphine (2 cats), and ether (1 cat). The results were substantially similar in all the animals. Occasionally the digitalis produced a rise in the carotid pressure, but the usual effect was a progressive fall—results similar to those described by Travell, Gold and Modell³³. In no instance, however, did the portal pressure show a rise during the injection of the digitalis bodies. The reactions in all the cats were consistent in showing a fall in portal pressure after about 25 or 30 per cent of the fatal dose had been injected. The fall continued until the heart stopped. During the asphyxia a rise usually took place. In 1 experiment on the dog with the same technic we obtained, on the contrary, a marked rise of the portal pressure, similar to the results reported by Dock and Tainter^{29a} and by Katz and his associates³⁰. Typical results are illustrated in figure 8.

Constriction of the hepatic veins by digitalis, therefore, does not occur in the cat and appears to be a phenomenon peculiar to the dog. Bauer, Dale, Poulsson and Richards³⁴ have shown that the liver of the dog possesses a special sluice mechanism not present in the cat. This sphincter mechanism near the caval openings of the hepatic veins in the dog responds to histamine by marked constriction. The anatomic counterpart of this physiologic difference is a heavier muscular coat in the hepatic veins of the dog than in those of the cat. The authors observed that "the hepatic veins in the human liver resemble those of the cat rather than those of the dog."

"TONE" HYPOTHESIS OF DIGITALIS ACTION

The hypothesis that digitalis increases the cardiac output in cases of heart failure by a direct action on cardiac tone receives its strongest support from the careful experiments of Cohn and his collaborators

32 Schmid, J. Beeinflussung von Druck und Stromvolumen in der Pfortader durch die Atmung und durch experimentelle Eingriffe, *Arch f d ges Physiol* **126** 165, 1909.

33 Travell, J., Gold, H., and Modell, W. Effect of Experimental Cardiac Infarction on Response to Digitalis, *Arch Int Med* **61** 184 (Feb.) 1938.

34 Bauer, W., Dale, H. H., Poulsson, L. T., and Richards, D. W. The Control of Circulation Through the Liver, *J Physiol* **74** 343, 1932.

Cohn and Stewart (1928) ⁷ observed in the dog that digitalis increased the excursion of the ventricular contraction (moving film) and reduced the size of the heart (roentgenogram) They ascribed the change in diastolic size to a direct action on tone and the change in excursion to a direct action on contraction and maintained that these two actions produce opposing results with respect to output, the action on size tending to reduce output and the action on contraction tending to increase it In subsequent papers, especially in the one by Cohn and Steele,³¹ the direct action on systolic contraction was accorded little consideration as a factor in the therapeutic action of digitalis, the "out-

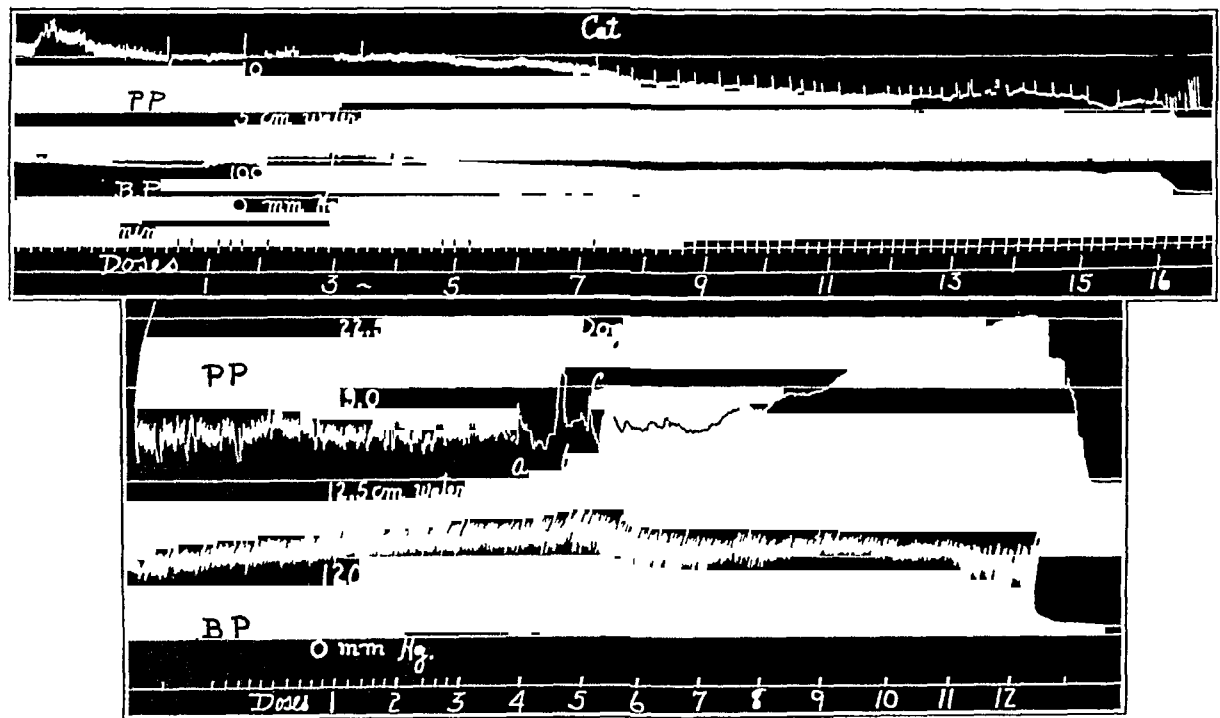


Fig 8—Effect of digitalis glucosides on the portal pressure in the cat and in the dog The upper tracing was made on a male cat weighing 3.64 Kg and anesthetized with ether Tincture of digitalis, diluted 1:10 was injected intravenously in doses of 5 per cent cat unit per kilogram every five minutes *P P* represents portal pressure, recorded in centimeters of water The cannula was inserted into the splenic vein at its junction with the portal vein, it was connected to a water manometer, which in turn was connected to a volume recorder *B P* represents carotid pressure, recorded in millimeters of mercury by a membrane manometer The lower tracing was made on a male dog weighing 6.63 Kg and anesthetized with soluble barbitol U S P (dose, 250 mg per kilogram, given intraperitoneally) and with morphine sulfate (dose, 5 mg per kilogram, given subcutaneously) Every five minutes 0.005 mg of ouabain per kilogram (5 per cent cat unit per kilogram) in a solution of 1:100,000 was injected Rises *a*, *b* and *c* are artefacts produced by tests for patency of the system In other respects the experiment was similar to the one on the cat

standing phenomenon," from which increased cardiac output followed in heart failure, being "an effect upon the tone of the heart" Stewart and his co-workers³⁵ have recently reaffirmed the belief that the change in cardiac output caused by digitalis is a consequence of its action in decreasing cardiac size. The evidence which they bring forth in support of that view, however, does not appear to exclude two alternative possibilities, one that the effect on size is entirely independent of that on systolic contraction and the other that the effect on size is secondary to improved contractility. The heart would become smaller as a result of the fact that the systole is stronger and the ventricle empties more completely.

The reasons for our belief that an action on tone (diastolic size) is not one by which digitalis abolishes heart failure are as follows:

1. Although in heart disease, and in heart failure particularly, the heart is larger than normal and its work is not commensurate with its size (Stewart and others³⁵), there is no reason for assuming that the function of the heart will be improved by reduction of its size, since there is no ground for belief that the fiber length is excessive in the sense of its being greater than is required for whatever work the muscle is capable of doing. The evidence indicates the contrary, namely, that clinical heart failure is not likely to involve overdistention of the heart muscle.

2. It is well known that the heart may become smaller through various indirect mechanisms (such as reduced size secondary to improved force, to diminished blood volume or to other peripheral actions) and that if these indirect possibilities are removed, as was the case in our studies on papillary muscle, the heart has no tendency to shorten its diastolic length (no increased tone) under the influence of digitalis at a time when its systolic force is increased several times.

Kabat and Visscher,³⁶ working with the turtle heart, have confirmed our observation that digitalis increases the capacity of the heart for work without change in tonus. They also arrived at a similar conclusion, namely, "that the theory, previously held, that the improvement in cardiac efficiency by digitalis glucosides is due even in part to changes in diastolic tonus, is without critical experimental foundation."

35 Stewart, H. J., Destricks, J. E., Crane, N. F., and Wheeler, C. H. Action of Digitalis in Uncompensated Heart Disease, *Arch. Int. Med.* **62**: 569 (Oct.) 1938.

36 Kabat, H., and Visscher, M. B. Influence of *k*-Strophanthosid on Elasticity of the Tortoise Ventricle, *Proc. Soc. Exper. Biol. & Med.* **40**: 8, 1939.

CONCLUSIONS

The results of experiments have been presented, and evidence has been adduced for the following statements regarding heart failure and the mechanism of digitalis action by which failure is abolished

1 The heart muscle is not overdistended in clinical heart failure. Dilatation of the heart is not usually an unfavorable phenomenon but an adaptive mechanism by which the failing heart maintains its optimum capacity for work

2 The high venous pressure in heart failure is not usually a cause but a result of heart failure. There is no sufficient reason for the belief that venous congestion of the order seen in clinical heart failure embarrasses the heart's contraction

3 Rapid heart rate in sinus rhythm and auricular fibrillation is usually not a cause but a result of heart failure

4 The effect of digitalis in abolishing heart failure is not mediated through any effect on rate in the average case, through action on the splanchnic circulation (constriction of hepatic veins) or through action on cardiac tone

5 Digitalis in therapeutic concentrations exerts no direct action on the so-called tone of mammalian heart muscle

6 Digitalis improves the function of the heart in heart failure by direct action on the heart muscle, which without primary change in the diastolic length of the muscle increases the tension which the muscle can develop during systolic contraction

COMPARATIVE STUDY OF VALVULAR CALCIFICATIONS IN RHEUMATIC AND IN NONRHEUMATIC HEART DISEASE

BERNARD S EPSTEIN, M D

BROOKLYN

The increasing frequency of the diagnosis of calcifications of the cardiac valves during life makes it desirable to discuss not only their causation but also their possible clinical significance

Thus far the greatest emphasis has been placed on calcifications of the aortic valve Christian¹ first indicated that aortic stenosis with calcification of the cusps might be regarded as a definite clinical entity, possibly of rheumatic origin Clawson, Noble and Lufkin² also stated that the clinical manifestations of the "calcified aortic nodular deformity" are sufficiently characteristic to warrant its designation as a separate entity, predominantly of a rheumatic nature Willius and Camp³ at first did not agree with the theory of a rheumatic causation, but after further investigation Dry and Willius⁴ concluded that the etiologic factor was rheumatic Other investigators, notably Monckeberg, Sohval and Gross and Margolies, Ziellessen and Barnes,⁵ stated the belief that calcification of the aortic valve is not of rheumatic origin Hamburger and Saphir⁶ found evidence for both a rheumatic and a nonrheumatic origin

From the clinical viewpoint, McGinn and White⁷ concluded that calcific deposits in the valves are relatively unimportant, except possibly

From the Montefiore Hospital for Chronic Diseases, New York, and the Jewish Hospital, Brooklyn

1 Christian, H A Aortic Stenosis with Calcification of the Cusps Distinct Clinical Entity, J A M A **97** 158 (July 18) 1931

2 Clawson, B J, Noble, J F, and Lufkin, N H The Calcified Nodular Deformity of the Aortic Valve, Am Heart J **15** 58, 1938

3 Willius, F A, and Camp, J D Clinical and Roentgenologic Comments on Calcareous Aortic Stenosis, M Clin North America **19** 487, 1935

4 Dry, T J, and Willius, F A Calcareous Disease of the Aortic Valve, Am Heart J **17** 138, 1939

5 Monckeberg, J G Der normale histologische Bau und die Sklerose der Aortenklappen, Virchows Arch f path Anat **176** 472, 1904 Sohval, A R, and Gross, L Calcific Sclerosis of the Aortic Valve (Monckeberg Type), Arch Path **22** 477 (Oct) 1936 Margolies, H M, Ziellessen, F O, and Barnes, A R Calcareous Aortic Valvular Disease, Am Heart J **6** 349, 1931

6 Hamburger, W W, and Saphir, O Aortic Stenosis, Mod Concepts Card Dis, 1939, vol 8, no 2

7 McGinn, S, and White, P D Clinical Observations on Aortic Stenosis, Am J M Sc **188** 1, 1934

as they influence the degree of valvular stenosis or aid in the roentgenographic identification of the lesions. Held and his co-workers⁸ regarded calcifications in the mitral valve as an additional factor in increasing the degree of stenosis in patients with "tight, non-regurgitant mitral stenosis." In general, calcifications of the mitral valve have received less detailed study than those of the aortic valve.

Since detailed information about calcifications of the mitral valve is scant and opinion concerning the role of rheumatic fever in producing calcifications of the aortic valve is varied, 148 consecutive cases of fatal rheumatic heart disease and 125 consecutive cases of nonrheumatic heart disease were reviewed from the following viewpoints: (1) The incidence and distribution of calcifications of the aortic and mitral valves, (2) the interrelationship, if any, between the presence of valvular calcifications and the duration of heart disease and symptoms of heart failure, (3) the

TABLE 1—*Classification of Cases of Rheumatic Heart Disease by Degree of Valvular Calcification*

Age Groups, Years	Mitral			Aortic			Mitral and Aortic		
	Slight	Moderate	Advanced	Slight	Moderate	Advanced	Slight	Moderate	Advanced
10-19	3	3	0	0	0	0	0	1	1
20-29	3	5	2	0	0	0	0	0	1*
30-39	2	2	3	1	1	0	0	0	1*
40-49	3	3	5	1	1	4	0	0	3
50 over	2	1	1	1	4	3	0	1	2

* Mitral, aortic and tricuspid valves were calcified

coincidence of valvular calcifications and pericarditis, disease of the coronary arteries, aortic calcification and electrocardiographic changes, and (4) the influence of valvular calcifications on the weight of the heart.

A comparison was made of the observations in the cases in which there were intracardiac calcifications and in those in which there were none.

RHEUMATIC HEART DISEASE

Calcifications were present in the valves of the heart in 64 of 148 patients. The degrees of calcification were designated as three types, "slight," "moderate" and "advanced," according to the relative amounts of lime salts found at autopsy (table 1). The age-sex incidence and the locations of the calcifications are set forth in table 2, and the weights

8 Held, I. W., Goldbloom, A. A., and Lieberman, A. Tight (Non-Regurgitant) Mitral Stenosis. A Clinico-Pathological Study, *Am J M Sc* **190** 791, 1935.

of the hearts, valvular defects and other pertinent data are presented in table 3. The age-sex incidence in the remainder of the patients is summarized in table 4.

Deposits limited to the mitral valve were observed in 38 patients. Mitral stenosis or a double mitral lesion was present in each patient in this group. The degree of valvular deformity did not necessarily parallel the degree of calcification. Pinpoint mitral ostiums occurred in hearts with minimal calcifications, as well as in those which had far more extensive deposits. Tight mitral stenosis, with leaflets of cartilaginous density, was not uncommon in patients who had no valvular calcifications, particularly those in the younger age groups. Extension of the calcifications into the annulus of the mitral valve was uncommon.

Calcifications limited to the aortic valve occurred in 16 patients. Eight others had calcifications of the mitral as well as of the aortic

TABLE 2—*Age-Sex Incidence and Location of Calcification in Cases of Rheumatic Heart Disease*

Age Groups	Total Number of Cases		Valvular Calcification					
			Mitral		Aortic		Mitral and Aortic	
	Male	Female	Male	Female	Male	Female	Male	Female
10-19 years	7	1	5	1	0	0	2	0
20-29 years	4	7	4	6	0	0	0	1
30-39 years	6	4	6	2	0	1	0	1
40-49 years	11	9	4	6	3	2	4	1
50 and over	9	6	2	2	4	3	3	1
Total	37	27						

valve, and 2 patients had extensive trivalvular deposits, involving the mitral, aortic and tricuspid valves. Twenty of these 26 patients were over 40 years old. Of the 6 patients under 40 years of age, 4 had calcifications in the aortic and mitral leaflets, and 2 had moderate calcific deposits in the aortic leaflets alone. The mitral valve was involved in 20 of the 26 patients, although calcifications of the mitral valve were not common in these persons. Twenty-four patients had definite deformities of the aortic valve. Eleven had aortic insufficiency, 10 had double aortic lesions, and 2 had aortic stenosis. Two patients, both over 50 years old, had calcifications limited to the annulus of the aortic valve, with no demonstrable defect of the valve.

Extension of the calcifications into the annulus of the aortic valve occurred in 8 patients, all over 40 years old. This apparently had not influenced the degree of valvular deformity appreciably.

A relative interdependence could be noted between the degree of calcification and the patient's age. Advanced calcifications limited to the mitral valve were infrequent prior to the age of 20. In the few cases

TABLE 3—Data for Cases of Rheumatic Heart Disease with Calcifications

Age Group, Yr	Valve Calcified	Degree of Calcification	Weight of Heart, Gm	Duration of Known Heart Disease, Yr	Duration of Cardiac Symptoms, Yr	Valvular Lesion*	Location of Calcific Deposits
10-19	Mitral	Slight	700	12	12	M S, M I, A S, A I	Scattered nodules on auricular surface of posterior leaflet of mitral valve
			500	8	8	T S, T I, M S, M I, A I, T I	Body of thickened posterior leaflet
			450	4	3	M S, M I, A I	At fused cusp of mitral valve
	Mitral and aortic	Moderate	290	10	1	M S, M I, A I	Auricular surface of greatly thickened anterior leaflet
		Moderate	270	9	10	M S, M I, A S, A I, T I	Multiple small areas of auricular surfaces of both leaflets
20-29	Mitral	Advanced	350	4	3	M S, M I, T S, T I, A I	Aortic cusp of mitral valve, aortic leaflet, descending the septum
			1,200	?	2	M S, M I, A I, T I	Anterior leaflet of mitral valve and in sinuses of Valsalva
			700	10	1	M S, M I, A I	Thick calcification with ulceration on mitral valve, thin deposits on aortic surface of aortic leaflets
			620	8	16	M S, M I, A I	Endocardium of left auricle just above insertion of posterior leaflet
			600	12	4	M S, M I, A S, A I, T S, T I	Small nodule on ring and auricular surface of mitral valve
	Mitral, aortic and tricuspid	Moderate	?	14	14	M S, M I	Auricular surface of valve
			750	13	8	M S, M I, A I	Posterior leaflet close to ring
			425	13	3	M S	At points of fusion of leaflets
			500	4	1	M S, M I, A S, A I, T S, T I	In ring and adjacent portion of leaflets
			600	7	7	Healed rheumatic endocarditis, mitral and pulmonary valves	Free edges of mitral leaflets
30-39	Mitral, aortic and tricuspid	Advanced	?	3	3	M S, M I	Endocardium of left auricle and adjacent auricular surface of leaflet
			500	10	?	M S	Fused rigid valve with calcifications in ring
			720	2	2	M S, M I, A I	Thick, heavy nodule in posterior leaflet
			600	16	3	M S, M I, A S, T S	All three leaflets stony hard
			?	17	7	M S, A I	Thin deposits fusing to form a small plaque
	Mitral	Slight	460	4	4	M S, M I	Auricular surfaces of valve
			600	2	2	M S, M I	Single nodule on auricular surface
			760	?	1	M S, M I, T I	Calcification at line of closure
			500	11	3	M S, M I, T S, T I	Posterior portion of leaflet, perforating leaflet and descending to ventricular endocardium
			350	?	?	M S, M I, A S, A I	Entire valve calcified
40-49	Aortic	Slight	440	2	?	M S, M I, T I	Aortic leaflet 9 mm thick
			1,000	29	3	M I, A I, A I	Slight deposits in sinuses of Valsalva
			800	1½	2	A S, A I	Papillary deposits descending to ventricular endocardium
			500	12	12	M S, M I, A I, T I	Mitral valve markedly calcified, aortic and tricuspid valves also calcified to a lesser degree

40-49	Mitral	Slight	680 390 300 720 580 700	23 2 10 12 2 2	23 0 8 12 2 2	M S, M I, A S, A I, T S, T I M S, M I, A I M S, M I M S, M I, A I M S, M I M S, M I	Small deposits on posterior leaflet Endocardium of left auricle and ring At line of closure Cusps and at points of fusion Body of leaflets Endocardium of left auricle descending to body of leaflets and free margins
		Advanced	350 400 550 630	5 3 2 4	5 3 2 4	M S, M I, A I M S, M I, A I M S, M I M S, M I	Entire posterior leaflet Fused commissure and rigid leaflets Both leaflets, extending on to ventricular surface Both leaflets Annulus of valve
	Aortic	Slight Advanced	300 320 500 700	1 5 40 16	1 7 10 16	M S, M I, A S, A I M S, M I, A I A S, A I M S, M I, A S, A I	Fusion of aortic cusps Leaflets, commissures and cusps Large deposits of calcium together with other prominent changes Partial calcification of all three leaflets All three leaflets
	Mitral and aortic	Moderate Advanced	450 620 450	2 3 5	2 2 5	M S, M I, A S, A I M S, M I, A S, A I M S, M I, A S, A I, T S, T I	Mitral ring, aortic cusps Mitral leaflets, aortic cusps and commissures Mitral leaflets, aortic commissures and cusps to a greater extent
			730	4	4	M S, M I, A S, A I	All aortic leaflets, posterior leaflet of mitral valve
50 and over	Mitral	Slight	450 550 500	? 1 4	? 1 4	M I, A S, A I M S, M I M S, M I	Tips of chordae tendineae Arteriosclerotic plaques on mitral leaflets Nodules on surface of posterior leaflet
	Aortic	Moderate Advanced Slight Moderate	180 850 500 400	10 3 5 ?	2 3 5 ?	M S, M I, A S, A I M S, M I A I M S, M I, A I	Calcified ring, calcifications extending into commissures At bases of leaflets At commissures of valves, in sinuses of Valsalva At commissures of valves, in sinuses of Valsalva Left anterior cusp of valve, extending up aorta
		Advanced	750 750 850 900	17 2 2 10	2 2 2 2	A S, M S M I, A I A S, M S M I, A I	All cusps of valve All cusps of valve All cusps of valve Pea sized nodule in posterior leaflet of mitral valve, healed rheumatic endocarditis aortic valve
	Mitral and aortic	Moderate Advanced	750 750 150 820	19 15 6 4	4 1 6 4	M S, M I, A I M S, M I, A I No defects M I, A S	Both annuli extending onto aortic leaflets Base of leaflets of both valves Aortic valve rigidly calcified, small calcifications of anterior leaflet of mitral valve

* In this table and in tables 5 and 6, A S and A I indicate aortic stenosis and aortic insufficiency, M S and M I, mitral stenosis and mitral insufficiency, T S and T I, tricuspid stenosis and tricuspid insufficiency

in which they were present, there were concomitant advanced calcification of the aortic valve and in 2 instances the tricuspid leaflets also were calcified. The infrequency of calcifications of the aortic valve before the age of 40 has been mentioned.

A relationship could not be established between the existence of valvular calcifications and the weight of the heart. Nor could a relationship be established between valvular calcifications and disease of the coronary arteries. This was most apparent in patients under 30 years of age, in whom extensive valvular calcifications existed in the presence of normal coronary vessels. Later in life, as the incidence of coronary sclerosis and arteriosclerosis increased, the relative frequency of calcifications of the aortic valve increased significantly.

The incidence of pericarditis was about the same in patients with and in those without valvular calcifications, occurring in 35 per cent of the former group and in 45 per cent of the latter. Only 4 patients with

TABLE 4—*Age-Sex Incidence in Cases of Rheumatic Heart Disease Without Intracardiac Calcifications*

Age, years	0-9	10-19	20-29	30-39	40-49	50 or Over
Male	8	14	14	4	6	6
Female	0	5	7	7	6	6

calcific deposits had changes indicative of recent pericarditis. Fresh pericarditis was more frequent during the first two decades of life, occurring in patients without calcifications.

The distribution of the calcifications in the valves is of interest. Minimal deposits occurred as small, thin calcific plaques or nodules in the auricular surfaces of the leaflets adjacent to their insertions. Encroachment of the calcifications on the endocardium of the left auricle immediately above the insertion of the leaflets was not uncommon. Deposits limited to the endocardium of the left auricle immediately above the insertion of the mitral leaflets were also seen. Minimal calcifications of the aortic valve were most frequent in the sinuses of Valsalva and at the commissures of the leaflets. The calcifications did not extend into the base of the aorta at any time.

The free edges of the valves were never involved when minimal calcifications were present. Moderate calcifications rarely involved the edges of the leaflets. Advanced calcifications, however, frequently involved the edges, although the thickest deposits were most common in the bodies of the leaflets.

A history of rheumatic fever was obtained from half the patients with calcific valves, and from 55 per cent of those without valvular calcifications. In both groups the number of positive histories decreased in the older age groups.

The physical characteristics of the murmurs were more consistent with the degree of valvular malformation than with the presence or degree of calcific deposits. The hearts with the most deformed valves presented the most exaggerated murmurs, whether or not calcifications had been superimposed. Deformities of similar degree, occurring with or without calcifications, set up murmurs of approximately similar characteristics. The possibility that calcifications set up heart sounds peculiar to themselves is not borne out by the data available here.

The electrocardiographic changes were those usually associated with active rheumatic heart disease or disease of the coronary arteries. The cause of death of almost every patient was congestive heart failure with terminal intractable decompensation. No instance of sudden death was noted, the term "sudden death" as used here implying that the patient had been in relatively good health for some time before death occurred unexpectedly. Since this series is drawn from a hospital devoted to the treatment of chronic diseases, it can be understood why sudden death was not observed.

HYPERTENSIVE AND ARTERIOSCLEROTIC HEART DISEASE

In order to compare the incidence, distribution and clinical picture of rheumatic and of nonrheumatic valvular calcifications, 125 consecutive cases of hypertensive and arteriosclerotic heart disease in which post-mortem examination was made were studied.

There were 84 men and 41 women in this series. Twelve were between 40 and 50 years old, and 22 were over 70. Eighty-three patients were known to have hypertension. The presence of preexistent hypertension had been mentioned as a clinical possibility in 15 of the remaining 42 patients. Well marked arteriosclerotic changes involving either the coronary arteries or the aorta or both were seen in almost every patient in this group.

Calcifications were present in the valves of 27 patients, each over 50 years old. They occurred in 16 men and in 11 women. The mitral valve alone was involved in 9 patients, the aortic valve alone in 12, the mitral and aortic valves in 4, the mitral, aortic and tricuspid valves in 1 and the mitral, aortic and pulmonary valves in 1.

Calcifications of the mitral valve were limited to the annulus in each of the 9 patients, they were considered as "advanced" in 7 patients and as "moderate" in the remaining 2. Mitral insufficiency was present in 1 patient. The others had anatomically competent valves. A soft systolic blow had been heard over the precordium in 3 patients, the heart sounds of the remaining patients had been considered normal. Seven had hypertension. One patient had advanced cardiac failure. Symptoms of

TABLE 5—*Calculations of the Mitral Valve in Cases of Hypertensive and Arteriosclerotic Heart Disease**

Age	Sex	Weight of Heart, Gm	Coronary Arteries	Aorta	Valvular Lesion	Murmurs	Blood Pressure	Duration of Cardiac Symptoms	Duration of Known Heart Disease	Congestive Heart Failure	Cause of Death
71	♀	320	Pipestem	Advanced arteriosclerosis	M I	Apical systolic	190/100	None	2 yr	None	Diabetic coma, bronchopneumonia
69	♀	640	Normal	Advanced arteriosclerosis	None	None	230/185	13 yr	13 yr	Slight	Cerebral accident
57	♂	510	Sclerotic, tortuous and narrow	Advanced arteriosclerosis	None	None	210/110	None	5 yr	None	Cerebral accident (?) pulmonary edema
75	♀	120	Normal	Moderate arteriosclerosis	None	Apical systolic	160/100	None	2 yr	None	Cerebral accident bronchopneumonia
65	♂	480	Sclerotic, old occlusion	Advanced arteriosclerosis	None	Apical systolic	200/110	2 yr	2 yr	Advanced	Congestive heart failure
73	♂	350	Normal	Normal	None	None	170/90	None	5 yr	None	Bilateral renal infection sepsis
68	♀	300	Sclerotic	Normal	None	None	None	None	None	None	Coronary occlusion †
57	♂	550	Normal	Normal	None	None	170/115	None	2 yr	Advanced	Congestive heart failure
75	♂	350	Normal	Normal	None	None	None	None	None	None	Carcinoma of the cecum

* All deposits were located in annulus

† Fibrinous pericarditis present

moderate cardiac embarrassment had been present in 2 others. In the remaining 6 patients the presence of organic heart disease had not been suspected, their only symptom had been hypertension.

In the 4 patients with calcifications of both the mitral and the aortic valve, those in the aortic valve were predominant. In all 4 the calcifications in the aortic valve were located chiefly in the annulus, and in 2 instances they extended to the cusps. The calcifications in the mitral valve, which were minimal in extent, were situated in the aortic cusp of the valve in 2 instances and in the annulus in the other 2. In all 4 patients the valvular defects were not extensive, and in 3 instances they had not been diagnosed before death.

Five of the 12 patients with calcifications limited to the aortic valve had valvular defects. Two had double aortic lesions, 2 had aortic insufficiency, and 1 had aortic stenosis. The calcific deposits were considered advanced in 4 of these patients. Of the remaining 7 patients, 3 had extensive calcifications without valvular defects. Characteristic murmurs had been present in the patients with incompetent valves. Several others had systolic murmurs of varying intensity, usually over the precordium. Congestive heart failure occurred with equal frequency in patients with and in those without valvular calcifications.

Anginal symptoms had been frequent both in the patients with and in those without calcifications of the aortic valve. Three patients, however, are noteworthy, as they had had definite anginal syndromes without demonstrable disease of the coronary arteries. All had extensive calcareous deposits deforming the cusps and encroaching into the ostiums of the coronary arteries.

The heaviest heart in this series, which weighed 850 Gm, was that of a man with hypertension and moderate calcifications in the bases of the aortic leaflets. The patients without hypertension had hearts which weighed less than 300 Gm. The remainder either had had hypertension or a history indicative of antecedent hypertension. The patients with well marked deposits in the aortic valve but without hypertension had hearts which weighed less than 450 Gm.

Pericarditis was uncommon. Only 3 patients in this series had evidences of old pericarditis. One patient with renal disease showed fresh pericarditic changes.

Fourteen of the 27 patients with valvular deposits had no clinical manifestations of heart failure. Of the remaining 13, 9 had had mild congestive failure for less than five years, and the remainder had had symptoms of heart failure for a longer time. Six of the 14 patients with heart failure had been known to have hypertension. The remainder had normal blood pressures. In general, the duration of cardiac symptoms approximated that of the known cardiac disease. There were no instances of sudden death.

TABLE 6—*Calcifications of the Aortic Valve in Cases of Hypertensive and Arteriosclerotic Heart Disease*

Age	Sex	Calcification	Weight of Heart, Gm	Coronary Arteries	Aorta	Valvular Lesions	Murmurs	Hyper tension	Dura- tion of Cardiac Symp- toms	Dura- tion of Known Heart Disease	Congestive Heart Failure	Cause of Death
76	♀	Advanced, in bases of leaflets	230	Slight sclerosis	Moderate arterio sclerosis	A S		None	None	None	None	Carcinoma vulvae with metastases*
70	♂	Advanced, in bases of leaflets	330	Slight sclerosis	Moderate arterio sclerosis	None	Apical systolic	None	8 mo	8 mo	Advanced	Leukemia
68	♂	Moderate nodule in posterior leaflet	320	Normal	Syphilitic aortitis	None	Short apical systolic	None	1 yr	1 yr	Moderate	Gangrene of left leg, bronchopneumonia
68	♂	Slight, in sinuses of Valsalva	600	Normal	Advanced arterio sclerosis	None	Short apical systolic	170/110	6 mo	12 yr	Advanced	Congestive heart failure
63	♂	Advanced, in bodies and free edges of leaflets	600	Normal	Moderate arterio sclerosis	A S, A I	Harsh systolic over precordium	None	8 yr	8 yr	Advanced	Pulmonary edema
68	♀	Advanced, in base of posterior leaflet	270	Normal	Normal	None	Blowing systolic over apex	None	None	None	None	Tuberculosis
58	♂	Advanced, at commissures of valve	400	Normal	Syphilitic aneurysm	A I	Aortic systolic and diastolic	180/50	None	None	None	Retropertitoneal sarcoma
57	♂	Slight, nodules at bases of leaflets	850	Rigid, thick	Marked arterio sclerosis	None	Apical systolic	190/100	None	9 yr	Advanced	Congestive heart failure
63	♂	Advanced, at commissures and cusps	500	Narrow, arterio sclerotic	Advanced arterio sclerosis	None	None	None	2 yr	2 yr	Advanced	Congestive heart failure
62	♂	Moderate, at commissures	600	Ostiums occluded by calcifications, vessels themselves negative	Syphilitic aortitis	A I	Aortic systolic and diastolic, mitral systolic	None	2 yr	2 yr	Moderate	Pulmonary edema, coronary occlusion (?)
67	♂	Advanced, at bases, extending into leaflets	470	Atheromatous	Moderate arterio sclerosis	A S A I	Harsh aortic systolic and diastolic	None	2 yr	2 yr	Moderate	Carcinoma of prostate
71	♂	Slight, in sinuses of Valsalva	250	Normal	Normal	None	None	None	None	2 yr	Advanced	Congestive heart failure

* Old pericarditis present

The electrocardiographic changes were those resulting from disease of the coronary arteries. Auricular fibrillation and partial bundle branch block were the most frequent arrhythmias. No changes which might be interpreted as indicative of calcifications of the aortic valve could be demonstrated.

COMMENT AND SUMMARY

Slight and moderate calcifications in the mitral valves of patients with rheumatic heart disease occurred most frequently in the leaflets. The free margins were often involved when the lesions were extensive. The smallest deposits were situated on the bodies of the leaflets or the endocardium of the left auricle adjacent to the insertion of the leaflets. Advanced valvular deformity was associated with the calcifications in almost every instance, regardless of the degree of calcification.

Calcifications of the aortic valve in patients with rheumatic heart disease who were under 30 years of age were accompanied in each instance by extensive changes and calcification in the mitral valve. In 2 persons the tricuspid valve was involved also.

The incidence of calcifications of the aortic valve rose sharply after the age of 40. The lesions of the aortic valve associated with the calcific deposits in older patients were usually less extensive than those in younger persons. Frequent association with lesions of the mitral valve was noted, but calcifications in the mitral leaflets in such persons were not common.

In patients with nonrheumatic heart disease calcifications of the mitral valve involved the annulus. Concomitant valvular defects were uncommon in this group. It is noteworthy that the auscultatory findings were within normal limits. This may indicate that the calcifications did not produce significant changes either in the anatomic function of the valve or in the heart sounds.

Calcifications of the aortic valve in nonrheumatic heart disease were equally frequent in the leaflets and in the annulus. In some instances both structures were involved. Aortic valvular defects due to calcific deposits were relatively frequent, but as a rule were not as extensive as those seen in cases of rheumatic heart disease with calcification of the valves. However, advanced calcifications of the aortic valve were present in patients who had had neither clinically demonstrable defects of the aortic valve nor symptoms of heart failure.

The weights of the hearts with calcified valves were independent of the presence of calcifications. Disease of the coronary arteries and aortic arteriosclerosis with calcification were more frequent in the nonrheumatic than in the rheumatic group. Nevertheless, patients with rheumatic heart disease who had survived the age of 40 had calcific deposits similar in extent and distribution to those of patients with nonrheumatic heart dis-

ease The incidence of calcifications of the aortic valve was definitely greater in the rheumatic group after the age of 40 It is reasonable to assume that the same process might be responsible for the calcifications in the two groups The possibility of calcification occurring on the site of an old rheumatic lesion, thereby speeding the disease process, has been mentioned

Pericarditis was more frequent in the rheumatic group, and may when present provide a clue pointing to a rheumatic origin

From the clinical viewpoint, the presence of calcifications in the heart valves did not appreciably alter the prognosis Nor did there seem to be any relationship between the duration of symptoms of heart failure or of known heart disease and the presence of calcareous deposits The symptoms of heart failure appeared to be related to the effect of the valvular deformity on the myocardium, and the degree of deformity apparently may be the same with or without calcareous deposits This is borne out by the similarity in the incidence of heart failure in patients with rheumatic heart disease and in those without valvular calcifications, as well as by the relatively low incidence of heart failure in the group with nonrheumatic heart disease with valvular calcifications

The lack of influence of calcifications in the valve on the heart sounds may best be represented by the absence of significant auscultatory changes in the patients with nonrheumatic heart disease associated with a calcified mitral annulus

ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH PERICARDITIS

PAUL H. NOTH, M.D.*

DETROIT

AND

ARLIE R. BARNES, M.D.

ROCHESTER, MINN.

There are more clinical conditions than are apparent on first consideration in the diagnosis of which a knowledge of the electrocardiographic patterns occurring in pericarditis may be helpful. It has been said often that the diagnosis of acute pericarditis is more often missed than made. When purulent pericarditis is present as a primary disease or as a complication of pleurisy or pulmonary disease it is especially important to make the diagnosis early so that surgical treatment may be instituted promptly. The postoperative occurrence of substernal or precordial pain, evidences of embarrassment of the circulation and a pericardial friction may provide a puzzling problem in differentiating between simple pericarditis and thrombosis of a coronary artery. The similarity between the electrocardiograms of the two conditions may lead to serious error unless the dissimilarities are appreciated. Pericarditis may also complicate acute rheumatic fever, cardiac wounds, pneumonia, uremia and occlusion of a coronary artery. In these instances the electrocardiographic pattern of pericarditis may be superimposed on that of the primary condition, and the resulting tracings can be properly evaluated only if this fact is borne in mind. Chronic constrictive pericarditis often has a characteristic electrocardiogram, which aids in its differentiation from hepatic cirrhosis and other conditions. The frequent spectacular results of pericardiectomy make this distinction important. Chronic tuberculous pericarditis may be discovered, because a suggestive electrocardiogram may lead one to secure other confirmatory evidence.

THE ELECTROCARDIOGRAM ASSOCIATED WITH EXPERIMENTAL PERICARDIAL LESIONS AND ACUTE AND SUBACUTE PERICARDITIS IN MAN

The literature on electrocardiograms characteristic of these lesions has grown rapidly, especially since 1929, and extensive reviews of it

From the Division of Medicine, the Mayo Clinic

*At the time this work was done Dr. Noth was a Fellow in Medicine, the Mayo Foundation.

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have appeared in articles by Schwab and Herrmann,¹ by Vander Veer and Norris² and by Winternitz and Langendorf³. We shall limit our remarks to the studies concerned with the elucidation of the theoretic mechanisms underlying the production of the electrocardiographic pattern of pericarditis and to certain other studies which have been insufficiently emphasized in other reviews or have appeared only recently.

Oppenheimer and Mann⁴ ascribed the low voltage of the electrocardiograms in cases of pericarditis with effusion to a short-circuiting effect of the fluid on the electric impulses originating in the heart. Katz, Feil and Scott⁵ studied the electrocardiographic changes produced by the injection of saline or oil solutions into the pericardial sac in dogs. They attributed the elevation of the ST segment and the changes in the T wave which occurred to generalized myocardial ischemia produced by the hydrostatic pressure of the pericardial fluid. Foulger and Foulger⁶ showed, under similar experimental conditions, that unless the intrapericardial pressure was maintained at a certain level, by increasing the amount of the injected fluid, the pericardium soon stretched enough to cause a fall in pressure and a return of the electrocardiogram to normal. They concluded that elevation of the RS-T segment in the electrocardiograms of patients suffering from pericardial effusion is an indication that the effusion is of recent origin or of such volume that the limits of relaxation of the pericardium have been reached.

Fowler, Rathe and Smith,⁷ in a noteworthy investigation, were able to correlate the changes in the T wave in experimental pericarditis with the inflammatory reaction in the subepicardial myocardium and

1 Schwab, E. H., and Herrmann, G. Alterations of the Electrocardiogram in Disease of the Pericardium, *Arch Int Med* **55** 917-941 (June) 1935.

2 Vander Veer, J. B., and Norris, R. F. The Electrocardiographic Changes in Acute Pericarditis. A Clinical and Pathological Study, *Am Heart J* **14** 31-50 (July) 1937.

3 Winternitz, M., and Langendorf, R. Das Elektrokardiogramm der Perikarditis, *Acta med Scandinav* **94** 141-188, 1938.

4 Oppenheimer, B. S., and Mann, H. An Electrocardiographic Sign in Pericardial Effusion, *Proc Soc Exper Biol & Med* **20** 431-432, 1923.

5 Katz, L. N., Feil, H. S., and Scott, R. W. The Electrocardiogram in Pericardial Effusion, *Am Heart J* **5** 77-83 (Oct) 1929.

6 Foulger, M., and Foulger, J. H. The Blood Pressure and Electrocardiogram in Experimental Pericardial Effusion, *Am Heart J* **7** 744-752 (Aug) 1932.

7 Fowler, W. M., Rathe, H. W., and Smith, F. M. The Electrocardiographic Changes Following the Ligation of the Small Branches of the Coronary Arteries, *Am Heart J* **8** 370-387 (Feb) 1933.

observed that when there was complete replacement of the portions involved in the inflammatory process by fibrous tissue the T waves had returned to normal. Bay, Gordon and Adams⁸ introduced fluid under pressure into the pericardial sac and obtained elevations in the RS-T segment and inversions of the T wave. They also partly occluded the superior and inferior venae cavae. When this was done without varying the intrapericardial pressure the marked elevations of the RS-T segment did not appear. They stated the belief that their experiments eliminated the consideration of interference with venous return, changes in temperature and chemical changes as factors in the production of the characteristic electrocardiogram.

Heimann and Schwab⁹ observed the electrocardiographic changes produced by two general types of experiments. First, electrocardiographic studies were made of goats and dogs during a period of increased intrapericardial pressure produced by injection of fluid into the pericardial sac, and second, electrocardiographic changes were observed over a period of weeks after the injection of irritating substances into the pericardial sac. The authors ascribed the well marked elevations of the RS-T segment seen in the experiments with increased intrapericardial pressure to the observed decrease in aortic and pulse pressures, which, by inference, were thought to lead to a decrease in the flow of blood in the coronary arteries, with consequent ischemia of the whole heart. In the experiments with irritating solutions they attributed the lesser degrees of elevation of the RS-T segment, as well as the later changes in the T wave, to the production of subepicardial myocarditis.

Vander Veer and Norris² reported on a pathologic study of the hearts of 10 patients whose fatal illnesses included in each instance acute pericarditis. In each of 6 instances in which the electrocardiograms were characteristic of pericarditis the authors observed extensive subepicardial myocarditis. Of 4 cases in which the electrocardiograms were not characteristic there were 3 in which the pericarditis did not penetrate into the subepicardium in any of the numerous sections studied and 1 in which there was penetration in only a few small regions. They concluded that the subepicardial myocarditis was the cause of the electrocardiographic pattern and that the lack of a consistent relation between the type of electrocardiogram and the presence or absence of pericardial effusion excluded the pericardial effusion as an etiologic factor in the cases observed by them.

8 Bay, E. B., Gordon, W., and Adams, W. Electrocardiographic and Blood Pressure Changes in Experimental Pericardial Effusion and Occlusion of the Venae Cavae, *Am Heart J* 8 525-532 (April) 1933.

9 Heimann, G., and Schwab, E. H. Some Experimental and Clinical Electrocardiographic Observations on R-S-T and T Changes in Pericarditis, *Tr A Am Physicians* 49 229-244, 1934.

Bellet and McMillan¹⁰ made histologic studies in 19 cases of pericarditis and concluded that the results together with certain clinical observations indicated that invasion of the subepicardial myocardium by the inflammatory process was chiefly responsible for the changes in the RS-T segment

Most writers on this subject do not mention the rather striking facts reported by Master¹¹ in a review of a series of cases selected on the basis of electrocardiograms in which T waves of low voltage were present. The pericardium was known to have been involved in 8 of 24 cases in which the condition was fatal. This is a notably high incidence of cases of pericarditis, when one considers that all types of cardiac disease were included and bears in mind that the basis of the selection was the occurrence of T waves of low voltage. Master also pointed out that pericarditis uncomplicated by myocardial disease could produce this phenomenon, since he had observed it in cases of tuberculous pericarditis and carcinoma of the pericardium in which autopsy revealed no evidence of myocardial involvement.

One of us (Barnes) and Mann,¹² in a study of the electrocardiographic pattern in experimental occlusion of the coronary arteries, performed control experiments in which the pericardium was merely incised and then sewed. The coronary arteries were not molested. Reciprocal deviation of the RS-T segments in leads I and III did not occur, but at a certain stage reversal of the normal direction of the T waves, resembling that seen in experimental occlusion of the coronary arteries, was observed. The only explanation of its occurrence was the presence of pericarditis, and it was pointed out that in a few days it obscured the initial electrocardiographic patterns produced by ligation of the coronary arteries.

Peel¹³ reported on the electrocardiograms of 48 patients with pericarditis. He stated the belief that the elevation of the RS-T segment was due to myocarditis rather than to the pericardial effusion, since he noted well marked elevation of the segment in the early dry stage of pericarditis which disappeared during the period when there was clinical evidence of the accumulation of fluid.

10 Bellet, S., and McMillan, T. M. Electrocardiographic Patterns in Acute Pericarditis. Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads, a Study of Fifty-Seven Cases, *Arch Int Med* **61** 381-400 (March) 1938.

11 Master, A. M. Low-Voltage T Waves in the Electrocardiogram, *Am J M Sc* **181** 211-217 (Feb.) 1931.

12 Barnes, A. R., and Mann, F. C. Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *Am Heart J* **7** 477-497 (April) 1932.

13 Peel, A. A. F. On the Occurrence of the So-Called "Coronary T Wave" in Electrocardiograms from Cases of Pericarditis, *Glasgow M J* **122** 149-166 (Oct.) 1934.

Schondorf¹⁴ called attention to the difference in the contour of the RS-T segment in pericarditis and in occlusion of the coronary arteries. In the former it is concave upward, while in the latter it is convex upward. This differential point applies only to the appearance during the period of RS-T elevation, since later the typical "cove plane" T waves, the so-called coronary T waves, may be seen in pericarditis.

Winternitz and Langendoif³ included in their series 10 cases of fatal purulent pericarditis, almost all of which had been observed a number of years previously. The diagnosis had been established before death in only 2 instances. The authors stated that if knowledge of the electrocardiographic pattern of pericarditis had existed at the time the patients had acute pericarditis, it would have been possible to make the diagnosis in 8 of the 10 cases and the subsequent institution of surgical measures might have altered the outcome in a number of instances.

THE ELECTROCARDIOGRAM IN CHRONIC PERICARDITIS

It has been generally appreciated only recently that adhesion of the pericardium to surrounding structures is in itself rarely productive of cardiac enlargement or embarrassment and is usually significant only when associated with thickening of and adhesions between the parietal and the visceral pericardial layer to the extent that a constrictive action on the heart results. There is no evidence that the chronic pericarditis commonly observed at autopsy, in which there is no appreciable thickening of the pericardial layers, has any clinical significance or characteristic electrocardiographic pattern. Therefore, two types of chronic pericarditis which are clinically important are considered, namely, chronic constrictive pericarditis and chronic tuberculous pericarditis. Since at times the latter may produce cardiac constriction, the two conditions are not entirely separate clinically. Since their electrocardiographic patterns may be indistinguishable (fig 1), they are considered together for the most part, although certain features distinctive of active chronic tuberculous pericarditis will be pointed out.

There are a number of reports of cases of constrictive pericarditis, in some of which pericardiectomy¹⁵ has been performed. The electro-

14 Schondorf, T. Ueber das Elektrokardiogramm bei Perikarditis, Verhandl d deutsch Gesellsch f inn Med **48** 350-354, 1936.

15 Bartels, E. C. Calcification of Pericardium, Minnesota Med **16** 205-207 (March) 1933. Burwell, C. S., and Flickinger, D. Obstructive Pericarditis. Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, Arch Int Med **56** 250-257 (Aug.) 1935. Flick, J. B., and Gibbon, J. H., Jr. Pericardiectomy for Advanced Pick's Disease, Arch Surg

cardiographic pattern in these cases was uniform. Our electrocardiographic observations in this group of cases were essentially in agreement with those previously reported and consisted usually of low voltage of the QRS complexes and of T waves which exhibited low voltage, were isoelectric or were inverted in various combinations in the standard leads. Auricular fibrillation was frequently present. Sprague¹⁶ summarized the electrocardiographic features in the cases observed at Massachusetts General Hospital by stating that in all there was either low voltage in the axial leads or inversion of T₁ and T₂ of the coronary type. Cushing and Feil¹⁷ reported 11 cases, in all of which the QRS complexes in the standard leads were of low voltage. The QRS complexes were usually slurred, but no instances of marked notching were present in the published tracings. The changes in the T waves were the same as those already mentioned. The P waves were normal voltage in all cases. In 7 cases there were precordial leads (leg and apex), and the electrodes were applied so that the T wave was normally directed downward. In 5 of these cases T₄ was upright. In 7 cases changes in position did not affect the electric axis, and in 3 others it was changed only slightly. After operation an increase in the amplitude of the QRS complex appeared in 4 of 7 cases.

The most extensive series of cases of chronic pericarditis studied electrocardiographically is that of 30 cases of tuberculous pericarditis reported by Harvey and Whitehill.¹⁸ Effusion was present in 15 cases. Low voltage of the QRS complex was observed in 11 of these. The voltage did not seem to depend solely on the amount of fluid present. In 1 instance the amplitude varied greatly from day to day when a considerable amount of fluid was present. A decrease in voltage after the removal of large quantities of fluid was seen in several cases, although there was usually an increase. A cove-shaped arching of the ST segment, usually ending in an inverted T wave, was present in 15

29 126-137 (July) 1934. Griswold, R. A. Chronic Cardiac Compression Due to Constricting Pericarditis. Relief by Pericardiectomy, with a Note on the Value of the Roentgenkymogram, *J. A. M. A.* **106** 1054-1057 (March 28) 1936. Ingvar, S. Five Cases of Operated Fibrous Pericarditis, *Acta med. Scandinav.* 1936, supp. 78, pp. 278-292. Sprague, H. B., and White, P. D. The Indications for and Results of Pericardial Resections. The Course of Five Cases, *M. Clin. North America* **15** 909-917 (Jan.) 1932.

16 Sprague, H. B. The Differential Diagnosis of Congestive Heart Failure and Constrictive Pericarditis (Pick's Disease), *Am. Heart J.* **12** 443-447 (Oct.) 1936.

17 Cushing, E. H., and Feil, H. S. Chronic Constrictive Pericarditis. Electrocardiographic and Clinical Studies, *Am. J. M. Sc.* **192** 327-334 (Sept.) 1936.

18 Harvey, A. M., and Whitehill, M. R. Tuberculous Pericarditis, *Medicine* **16** 45-94 (Feb.) 1937.

cases in lead I, in 17 cases in lead II and in 3 cases in lead III. An ST segment of opposite contour, with a slight downward concavity, was present in lead III in 3 cases in which the arched ST segment was present in lead I, a pattern closely resembling the change seen after infarction of the anterior apical portion of the left ventricle. The extent of elevation or depression of the ST segments was not stated. Inversion of the T wave was most commonly found in leads I and II, while the deflection remained upright in lead III or became diphasic.

In cases in which there was a precordial lead (apex and left leg) the voltage of the QRS complex was sometimes normal when it was low in the standard leads. In 7 cases there was a reversal of the normal direction of the T wave in the precordial lead. In 6 of 10 cases observed from seven months to six years after the onset of pericarditis the only abnormality found in this lead was absence of the Q wave. The T wave in the precordial lead usually returned to its normal position several weeks earlier than in the standard leads.

Harvey and Whitehill¹⁸ observed that the inversion of the T wave, especially in leads I and II, may be of prognostic import and that the evolution of the changes in this portion of the electrocardiogram may serve as a guide in the treatment of the patients. Reversion of the T wave toward or to normal was considered of good prognostic import. The authors advised that rigid restriction of activities and general care be continued as long as inversion of the T wave persists.

The electrocardiographic pattern observed in 1 case of proved tuberculous pericarditis studied in the present series revealed changes that were essentially like those observed in chronic constrictive pericarditis. In 2 additional cases of tuberculous pericarditis observed recently similar electrocardiographic changes (fig 1) have been shown.

REVIEW OF REPORTS DEALING WITH THE ELECTROCARDIOGRAM IN PERICARDITIS COMPLICATING OTHER CONDITIONS

Acute Rheumatic Fever—That pericarditis is a more frequent accompaniment of acute rheumatic carditis than is generally appreciated was emphasized by Friedberg and Gross,¹⁹ who found that the hearts of 28 (70 per cent) of 40 patients dying of cardiac failure during acute rheumatic fever showed grossly distinguishable universal pericarditis, while all of them showed microscopic evidence of pericarditis.

Most of the reports on the electrocardiograms of groups of patients with acute rheumatic carditis were published in the years before the electrocardiographic pattern of pericarditis was generally known. In many of the instances reported it is impossible, because of the lack

¹⁹ Friedberg, C. K., and Gross, L. Pericardial Lesions in Rheumatic Fever. *Am J Path* **12**: 183-204 (March) 1936.

of detailed clinical data, to be certain whether or not pericarditis was present. Some of the electrocardiograms alleged to show the most marked evidence of myocardial damage or involvement of the coronary arteries by the rheumatic process were characteristic of pericarditis, and the presence of pericarditis was frequently mentioned in the protocols of the cases. Lukomski²⁰ is the only author who described electrocardiograms with many characteristics of pericarditis and who stated that there was no clinical evidence of pericarditis in the reported cases. Only pathologic study could be regarded as excluding pericarditis with certainty in such cases.

Winternitz and Langendorf³ stated that there have been no reported instances of the occurrence of the electrocardiographic pattern of peri-

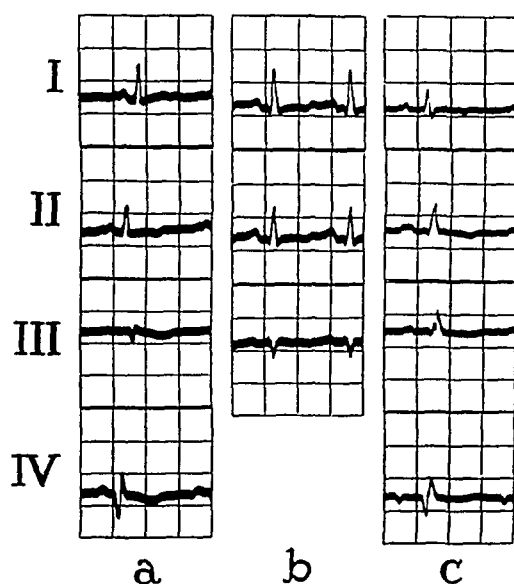


Fig 1—The electrocardiographic changes observed in these 3 patients with tuberculous pericarditis are the same as those observed in chronic constrictive pericarditis of undetermined origin and give no clue as to the tuberculous nature of the process.

(a) Standard electrocardiogram and tracing from the fourth lead obtained in a patient with chronic constrictive pericarditis. When a pericardiectomy was performed 750 cc of fluid was found in the pericardial sac. The pathologic diagnosis on the basis of specimens removed from the pericardium was tuberculosis.

(b) Standard electrocardiogram obtained in a patient with pericarditis. At necropsy the diagnosis was cardiac hypertrophy and chronic tuberculous pericarditis.

(c) A standard electrocardiogram and tracing from the fourth lead obtained in a patient whose clinical history strongly suggested the presence of tuberculous pericarditis.

20 Lukomski, P. Elektrokardiographische Beobachtungen bei akutem Rheumatismus, *Deutsches Arch f klin Med* **174** 268-288 (Nov) 1932.

carditis in cases of acute rheumatic carditis in which it had been shown pathologically that there was no pericarditis. In the 18 cases of rheumatic pericarditis the form of the electrocardiogram was independent of the amount of effusion, and the appearance of the features characteristic of pericarditis coincided with that of the other clinical evidences of pericarditis and was not related to the general course of the rheumatic myocarditis. The authors did not deny that it is possible that the electrocardiographic alterations in rheumatic pericarditis may be an expression of involvement of the myocardium by the pericarditis. The electrocardiograms in all of the 8 cases in which tracings were obtained repeatedly went through the stage of inversion of the T wave to restitution of a normal appearance between the fifth and the thirteenth week.

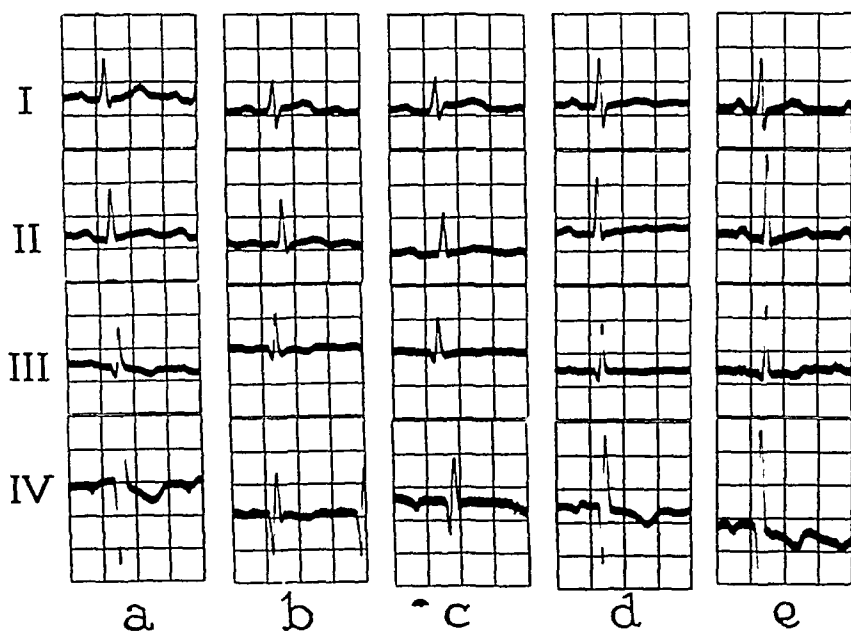


Fig 2—Electrocardiograms were obtained for a patient with rheumatic pericarditis with probable effusion (a) on February 25, (b) on February 26, (c) on February 27, (d) on April 9 and (e) on August 19. The patient complained of pain in the chest, and friction rub was heard first on February 25. Note the minimal deviation of the RS-T segments, the evolution of the changes in the T waves, and the stage at which the T waves tend to be isoelectric (c and d).

Since pericarditis has such a great incidence in cases of rheumatic heart disease and since its existence can be excluded only by necropsy, it is never safe to exclude pericarditis as an explanation of deviation of the RS-T segment or of changes in the T wave in the electrograms of patients with rheumatic fever. Figure 2 illustrates the changes observed in such a case and the eventual return to normal of the electrocardiogram after several weeks.

Wounds of the Heart—Electrocardiographic studies following operations for wounds of the heart contain few references to the role of pericarditis in the production of the observed electrocardiograms, although it is obvious that pericarditis is always present as a result of the operative incision of the pericardium, the escape of blood into the pericardial sac or the introduction of infection by the object causing the wound. Furthermore, most authors have not distinguished between the electrocardiograms of patients with damage to the left coronary artery (which was the artery involved in all but 1 instance) and the electrocardiograms of patients with no damage to the major divisions of the coronary artery. The latter point may seem irrelevant to a demonstration of the role of pericarditis in the electrocardiographic pattern. However, it seems that the best approach to interpretation of the role of any one pathologic process in this situation is to search for the characteristic effects of all the processes which might conceivably be reflected in the electrocardiograms.

Both pericarditis and acute cardiac infarction are known to affect the electrocardiogram in ways which are usually characteristic. The combined effect has been observed and reported after experimental ligation of a coronary artery,¹² as well as in cases of the complication of cardiac infarction by pericarditis.²¹ The electrocardiographic effect of a wound involving in most cases only a small portion of cardiac muscle has not been established. To disregard the influence on the electrocardiogram of the myocardial infarction consequent to severance of a coronary artery and pericarditis and to attribute the changes in the electrocardiograms in these cases to the myocardial damage of the wound does not seem reasonable. Careful scrutiny of the electrocardiograms in cases of cardiac wounds in which there was incidental involvement of the left coronary artery and in cases in which there was not such involvement reveals slight but definite differences. A review of reported instances in which electrocardiograms were obtained during the period after operation, when diagnostic deviations of the RS-T segment might be expected, reveals the following differences in the two groups of cases.

In the 3 cases in which there was involvement of the left coronary artery a depression of the RS-T segment in lead III reciprocal to elevation of this segment in lead I was present at some time.²² In

21 Winternitz and Langendorf.³ Barnes and Mann.¹²

22 (a) Elkin, D. C., and Phillips, H. S. Stab Wound of the Heart. Electrocardiographic Studies of Two Cases, *J. Thoracic Surg.* **1** 113-123 (Dec.) 1931. (b) Purks, W. K. The Electrocardiographic Findings Following Ligation of the Descending Branch of the Left Coronary Artery in Man, *Am. Heart J.* **7** 101-105 (Oct.) 1931. (c) Porter, W. B., and Bigger, I. A. Nonfatal Stab Wounds of the Ventricle, with Electrocardiographic Signs of Coronary Thrombosis and Absence of Anginal Pain, *Am. J. M. Sc.* **184** 799-804 (Dec.) 1932.

the 6 cases in which there was no involvement of the coronary artery this reciprocal depression of the RS-T segment in lead III was always absent ²³

A review of reported instances in which electrocardiograms were obtained during the period after operation, when inversion of the T wave might be expected to occur, reveals the following differences in the two groups of cases

In only 3 of 7 cases in which there was involvement of a coronary artery was there inversion of the T waves in all three standard leads ²⁴ The experimental studies of Mann and one of us (Barnes) ¹² indicated that in these 3 cases the effects of pericarditis on the electrocardiogram overshadowed the effects of severance of the coronary artery

In all 6 cases in which there was no involvement of the coronary artery there was inversion of the T waves in all three standard leads, ²⁵ presumably the result of the pericarditis that always is present in such cases

The failure of the T waves to become inverted in the three standard leads in 4 of the 7 cases in which there was involvement of the left coronary artery may be interpreted as illustrating the persistence of the tendency toward a reciprocal direction of the T waves in leads I and III as a consequence of cardiac infarction

From a practical standpoint, the important point is that the electrocardiogram may serve a useful purpose in determining in the presence of a wound in the precordial region whether or not the heart is involved and may give some information as to whether a branch of the left coronary artery has been severed

23 (a) Bates, W, and Talley, J E The Electrocardiograms of Coronary Occlusion Following a Stab Wound in the Left Ventricle, *Am Heart J* **5** 232-237 (Dec) 1929 (b) Koucky, J D, and Milles, G Stab Wounds of the Heart A Study of Electrocardiographic Changes, Polyserositis (Pick's Syndrome) and Pericarditis, *Arch Int Med* **56** 281-296 (Aug) 1935 (c) Eakin, W W The Removal of a Large Needle from the Heart with Electrocardiographic Changes in Rhythm During Operation, *Am Heart J* **8** 540-547 (April) 1933 (d) Warthen, H J Stab Wound of the Heart Report of a Case, *Ann Surg* **102** 147-152 (July) 1935 (e) Benet, G, and Spivey, C G Suture of Stab Wound of the Heart Report of Case, *J A M A* **104** 1979-1981 (June 1) 1935 (f) Porter and Bigger ^{22c}

24 Davenport, G L Suture of Wound of the Heart Ligating the Interventricular Branch of the Left Coronary Artery and Vein, *J A M A* **82** 1840-1845 (June 7) 1924 Oppolzer, R Heilung eines Herzdurchschusses mit Durchtrennung des hinteren absteigenden Astes der rechten Coronararterie nebst elektrokardiographischer Verfolgung, *Deutsche Ztschr f Chir* **242** 620-627 (March) 1934 Kment, cited by Oppolzer

25 Scherf, D Ein elektrokardiographisches Zeichen bei Erguss in Herzbeutel, *Wien med Wchnschr* **43** 298-300 (March) 1930 Elkin and Phillips ^{22a} Porter and Bigger ^{22c} Bates and Talley ^{23a} Koucky and Milles ^{23b} Eakin ^{23c}

Uremia—Although the recognition of pericarditis in cases of uremia is not of great clinical importance, the appreciation of the source of the electrocardiographic changes is of considerable interest. The second case reported by Wood and White²⁶ illustrates the superimposition of the pattern of pericarditis on the previous pattern of marked left ventricular strain. While in the first tracing the RS-T segment in lead I is depressed and the T wave is sharply inverted, in the tracing obtained after the onset of pericarditis there is marked elevation of the RS-T segment in leads I and II, with upright and accentuated T waves (compare fig 3*a* and *b*). Levine²⁷ published the tracings in a case in which there was elevation in the three standard leads, whereas in the previous tracing the RS-T segments had been isoelectric. Richter and O'Hare²⁸ reported electrocardiographic studies in 38 cases of uremia. Prior to the onset of pericarditis there were only "minor changes." Of 8 cases in which electrocardiograms had been taken after pericarditis had developed the electrocardiograms of 7 were abnormal: transient auricular fibrillation and auricular flutter in 2 cases, ectopic beats in 3 cases and a transient prolonged PR interval in 1 case. There was elevation of the RS-T segment in 2 cases, in the three standard leads in 1 and in leads I and II in the other.

In our cases uremic pericarditis indicated its presence in the electrocardiogram by one or two fairly diagnostic changes. The most significant change consisted of elevation of the RS-T segment in leads I and II. This change is frequently superimposed on the electrocardiogram of hypertension (fig 3). The second change concerned the T wave, which became negative with little or no deviation of the RS-T segment (fig 4*a* and *b*).

Pneumonia—Pyrah and Pain²⁹ stated that in a pathologic study of the hearts in 45 cases of purulent pericarditis associated with pneumonia and empyema there was complete absence of any acute lesion in the cardiac muscle or in the coronary vessels. This observation is in marked contrast to the pericarditis observed in pyemic processes, such as osteomyelitis, which is often dependent on a tiny abscess or septic infarct in the myocardium. The authors²⁹ did not specifically mention the condition of the subepicardial myocardium, although it

26 Wood, J. E., Jr., and White, P. D. The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, *Am J M Sc* **169** 76-87 (Jan.) 1925

27 Levine, S. A. Coronary Thrombosis. Its Various Clinical Features, *Medicine* **8** 245-418 (Sept.) 1929

28 Richter, A. B., and O'Hare, J. P. The Heart in Chronic Glomerular Nephritis, *New England J Med* **214** 824-830 (April 23) 1936

29 Pyrah, L. N., and Pain, A. B. Acute Suppurative Pericarditis. Two Cases Successfully Treated by Operation, *Lancet* **1** 905-908 (April 29) 1933

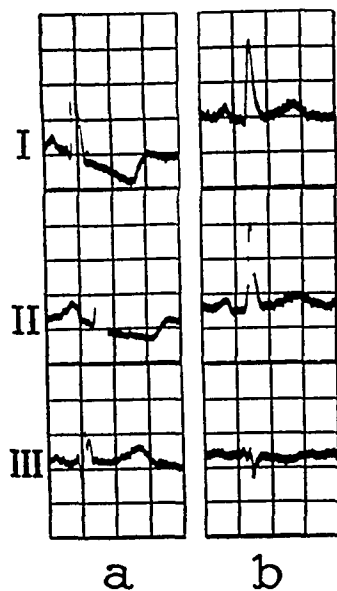


Fig 3—Electrocardiograms of a patient with uremia and severe hypertension (a) taken before the appearance of clinical signs of pericarditis and (b) taken at the time clinical evidence of uremic pericarditis was present

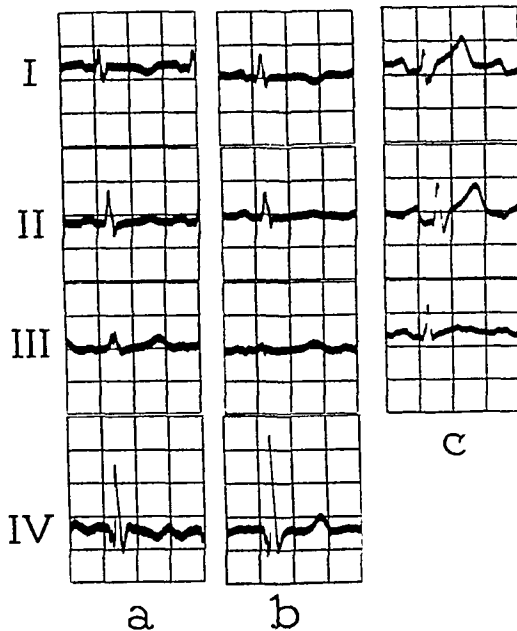


Fig 4—Standard electrocardiograms and tracings from the fourth lead (a) and (b) were taken forty-eight hours apart in the case of a youth aged 19 with uremic pericarditis and clinical evidence of accumulating pericardial fluid. In spite of evidence of pericardial effusion, elevation of the RS-T segment did not occur. Except for the preservation of Q_4 , the tracing looks like a late electrocardiographic relic of infarction of the anterior portion of the left ventricle.

Standard electrocardiogram (c) was obtained in a second patient with acute pericarditis and signs of increasing pericardial effusion. The elevation of the RT segment is almost totally confined to leads I and II. Note, however, the absence of depression in the ST segment in lead III, such as would be expected if acute infarction of the anterior portion of the left ventricle were present. Note the almost straight line of the anterior limb of the RT segment in leads I and II and the marked exaggeration of the T waves.

can hardly be doubted that there was some extension of the inflammatory process into this region in many of the cases. However, the absence of involvement of the myocardium as a whole, as well as of the coronary vessels, in pericarditis complicating pneumonia and empyema strengthens the conception that the electrocardiogram is influenced mostly by the inflammatory process in the pericardium and subjacent tissues.

Although some type of change in the RS-T segment is reported in a considerable number of cases of pneumonia, the extent of this change is not mentioned. Master, Romanoff and Jaffe³⁰ reported the occurrence of changes in the RS-T segment in 93 per cent of their cases. To judge from their published electrocardiograms, among which there was only one showing well marked elevation of the RS-T segment, in a case of acute fibrinopurulent pericarditis, observed at necropsy, the changes in the RS-T segment in most cases were probably only slight. In the case of pericarditis the coronary arteries were normal, and the administration of oxygen had no effect on the level of the RS-T segment. In a case reported by Shearer³¹ in which clinical evidence of pericarditis was absent but there were marked monophasic RS-T segments in leads I and II, this appearance persisted long after all evident cyanosis had disappeared. Although several authors³² have reported on electrocardiographic studies in sizable numbers of cases of pneumonia, the relation of the tracings to the possible presence of pericarditis cannot be determined satisfactorily because the occurrence of pericarditis is not specifically mentioned and because the number of electrocardiograms in each case is usually not recorded. Winternitz and Langendorf³ stated that they had never seen the electrocardiographic pattern of pericarditis in cases of pneumonia and pleurisy when clinical evidence of pericarditis was lacking, nor had they found reports of cases in which the electrocardiogram was characteristic of pericarditis but evidence of the complication was not seen at autopsy.

Cardiac Infarction—One of us (A. R. B.)³³ reported electrocardiographic observations in several cases of pericarditis complicating

30 Master, A. M., Romanoff, A., and Jaffe, H. Electrocardiographic Changes in Pneumonia, *Am Heart J* **6** 696-709 (June) 1931.

31 Shearer, M. C. "Plateau R-T" in a Case of Lobar Pneumonia, *Am Heart J* **5** 801-805 (Aug.) 1930.

32 DeGraff, A. C., Travell, J. G., and Yager, J. A. An Electrocardiographic Study of the Heart in Lobar Pneumonia, *J Clin Investigation* **10** 633-651 (Aug.) 1931. Abt, A. F., and Vinnecour, M. I. Electrocardiographic Studies During Pneumonia in Infants and in Children, *Am J Dis Child* **47** 737-749 (April) 1934. Krinski, L. Beobachtungen über Elektrokardiographie bei Pneumonie, *Ztschr f klin Med* **128** 27-37, 1935.

33 Barnes, A. R. Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis. Report of Cases, *Am Heart J* **9** 734-741 (Aug.) 1934.

cardiac infarction The features of the electrocardiograms in these instances included, in the early stage, elevation of the RS-T segment in the three standard leads and, somewhat later, either disappearance of the visible effects of the pericarditis, leaving a typical T_1 (fig 5*a* and *b*) or T_2 pattern, or persistence of the effect of the pericarditis, as evidenced by an inversion of the T wave in the three standard leads (fig 5*c*, *d* and *e*)

Winternitz and Langendorf³ mentioned three other causes of elevation of the RS-T segment in the three standard leads in instances of cardiac infarction First, when an infarction of the anterior apical region of the left ventricle occurs in association with bundle branch block of the common type, the RS-T segment may be elevated in the three standard leads This elevation in the first two leads is a part of the usual pattern of infarction in this location, and in the third lead

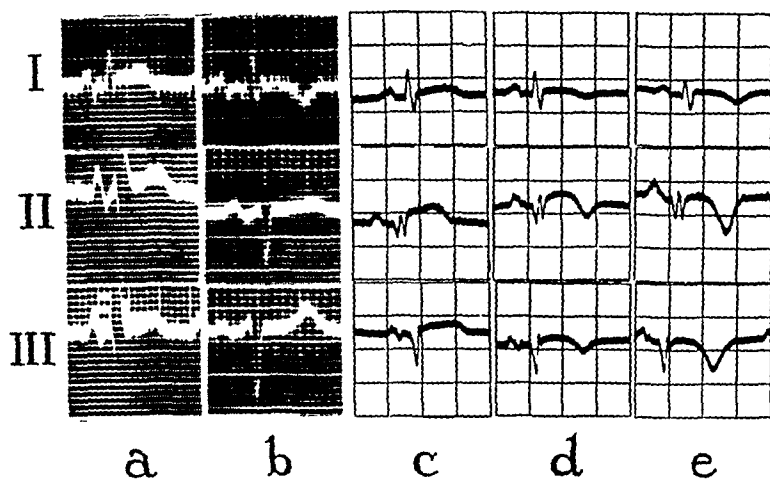


Fig 5—In a case of pericarditis complicating acute coronary occlusion electrocardiogram *a* was taken seven days after acute coronary occlusion and at a time when a pericardial friction rub was present Electrocardiogram *b*, taken fourteen days later, shows return to a typical late T wave in lead I, a relic of acute infarction of the anterior portion of the left ventricle The patient died of pneumonia sixteen months later Necropsy revealed that the pericardial sac was completely obliterated by adhesions An old healed infarct occupied the anterior portion of the left ventricle Electrocardiogram *c* was taken in a second case seven days after acute coronary occlusion, at a time when a pericardial friction rub was present Electrocardiograms *d* and *e* in the same case were taken eleven and twenty-six days, respectively, after coronary occlusion At autopsy, five and a half months later, the pericardium was adherent except over the posterior surface of the heart The lower anterior two thirds of the left ventricle was the site of an old healed infarct³³

it is due to the usual elevation of this segment associated with the frequent type of bundle branch block Second, when there is a previous pattern of left ventricular strain, the RS-T segment may retain the

elevation in the third lead seen in this condition and may become elevated in the first and second leads, as seen in cases of anterior infarction. Third, when there is combined anterior and posterior infarction there may be present a Q wave in lead I, a small R wave in lead I, no Q wave in the precordial lead (taken by the Wolfarth method) and lengthened Q waves in leads II and III. Winternitz and Langendorf³ expressed the opinion that elevation of the RS-T segment in all three leads, if accompanied by these changes, should be considered as due to combined infarction.

ANALYSIS OF MATERIAL

The material for this study is composed of a series of cases in which autopsies were performed and a clinical series of cases in which electrocardiograms were obtained during a period when pericarditis was present, as determined from the protocols. The autopsy series includes all cases studied in the department of pathology from 1929 to 1936, inclusive, with a few additional cases. The clinical material includes all cases observed from 1929 to 1937, inclusive, and a few additional cases seen in 1937. The large number of cases in which chronic pericarditis apparently was only an incidental observation at autopsy were not studied in detail because of the frequency with which this phenomenon is observed and its well known lack of clinical significance.

The matter of the presence or absence of a pericardial effusion was considered carefully in each case because of the hypothesis of its relation to the production of the electrocardiogram characteristic of pericarditis. The presence of an effusion is stated as proved only when fluid was aspirated from the pericardial sac during life or was observed at necropsy. The presence of an effusion is considered as probable when there was positive roentgenographic evidence or physical signs, such as shifting cardiac borders or fluctuation of the audibility of heart sounds. In the cases classified as those in which there was no known effusion this clinical evidence was lacking, no fluid was observed at necropsy, which was performed within a sufficiently short time after the period of clinical observation that the disappearance of an effusion would have been impossible or highly improbable.

Also, since the stage of pericarditis has an important bearing on the electrocardiographic observations, the cases were divided into groups in which the condition was acute, subacute or chronic, and for those in which the stage of the condition could not be determined from the history or pathologic study a separate group, stage indeterminate, was made. Table 1 classifies the cases in this manner.

In 25 cases necropsy was performed, and in 28 there was no necropsy. Table 2 classifies the cases according to causation.

METHOD AND STANDARDS OF ANALYSIS OF ELECTROCARDIOGRAMS

RS-T Segment—The RS-T segment is that portion of the electrocardiogram lying between the descending limb of the QRS complex and the T wave. It was measured with regard to its elevation above or its depression below the isoelectric line. According to the criteria of Pardee,³⁴ this segment normally may be elevated as

TABLE 1—*Frequency Distribution of Cases of Pericarditis According to Stage of the Disease and Presence or Absence of Effusion*

	Number of Cases
Acute pericarditis	
(a) Proved effusion	2
(b) Probable effusion	6
(c) No known effusion	11
(d) No effusion	13
Subacute pericarditis	
(a) Probable effusion	1
(b) No known effusion	2
(c) No effusion	1
Chronic pericarditis	
(a) Calcified pericardium	9
(b) Chronic tuberculous pericarditis	1
Pericarditis, stage indeterminate	
(a) Proved effusion	3
(b) Probable effusion	2
(c) No known effusion	1
Hematopericardium	1

TABLE 2—*Frequency Distribution of Cases of Pericarditis According to Causation*

	Number of Cases
Acute, subacute and indeterminate stages	
Chronic renal disease with uremia	10
Acute rheumatic fever	9
Postoperative pericarditis	5
Tuberculosis	1
Probable tuberculosis	1
Carcinoma involving the pericardium	2
Osteomyelitis with staphylococcal septicemia	1
Terminal	1
Lobar pneumonia	1
Bronchopneumonia	1
Pleurisy	2
Associated with bronchopneumonia, probably rheumatic in origin	1
Unknown	7
Chronic stage	
Indeterminate	9
Tuberculosis	1
Hematopericardium (ruptured arteriosclerotic aneurysm of the aorta)	1

much as 1 mm above the isoelectric line in occasional instances. In our study an elevation of the RS-T segment was recorded if it was 1 mm or more. Since the RS-T pattern shifted in some cases, the total number of changes in the RS-T segment listed exceeds the number of cases.

T Wave—The direction, height and contour of the T waves in each lead were observed. The term dome refers to a T wave of lowered voltage with a gradual

34 Pardee, H. E. B. *Clinical Aspects of the Electrocardiogram. A Manual for Physicians and Students*, ed. 2, New York, Paul B. Hoeber, Inc., 1928.

ascent and a somewhat prolonged, flattened summit, followed by a gradual descent to the isoelectric line. In cases in which there are several tracings the pattern of the T wave may show considerable variation. Each pattern is listed separately. Therefore, the total number of T wave patterns listed exceeds the number of cases.

QRS Complex—The amplitude of the QRS complexes was measured. Low voltage was considered to be present when the R wave was less than 5 mm in height in the three standard leads. The presence of Q waves in leads I and III was noted, and the tracings were analyzed as to whether there were also present the Q_1 and Q_s patterns which are known to occur at times in cases of myocardial infarction.

Precordial Lead—The precordial lead was an anteroposterior lead with the anterior electrode connected with the cable on the right arm and placed in the fourth intercostal space at a point midway between the left border of the sternum and the midclavicular line, the posterior electrode was connected with the cable on the left arm and placed just below the angle of the left scapula. In this lead there is normally present a Q wave of at least 1.4 mm in depth. The T wave is directed downward in tracings for normal adults, but is upright in a large proportion of tracings for children, being present more frequently in the younger age groups. A T wave of less than 3 mm in depth is classified as a shallow inversion. A T wave of more than 7 mm in depth is classified as an exaggerated inversion. The RS-T segment may be depressed as much as 2 mm and elevated as much as 0.5 mm. The normal limit below which low voltage may be said to be present has not been defined. Measurements are made by adding together Q and R. The lead is variously referred to as the precordial lead and the fourth lead.

CLASSIFICATION OF ELECTROCARDIOGRAMS ACCORDING TO DIAGNOSTIC SIGNIFICANCE

The electrocardiograms in this series of cases may be divided into four groups in respect to the extent to which they exhibit the features known to be characteristic of pericarditis. The first group of electrocardiograms, designated as pathognomonic, includes those showing a combination of features which, at present, is not known to occur in conditions other than pericarditis. The second group, designated as strongly suggestive, is composed of the electrocardiograms with features which are suggestive of pericarditis and which, when considered with the clinical features of the case, are of corroborative or diagnostic significance. In the third group, designated as suggestive, are those which are less definitely suggestive of pericarditis. The fourth group of tracings shows features not suggestive of pericarditis.

The case records were reviewed with regard to whether or not digitalis had been taken during the period in which its electrocardiographic effects might be present. The electrocardiograms were then carefully scrutinized for any evidence of such an effect. Such changes were found in only 2 cases.

OBSERVATIONS IN THE STANDARD LEADS

In 3 of the 53 cases the electrocardiograms were pathognomonic of pericarditis, in 22 they were strongly suggestive of pericarditis, in 11 they were only suggestive of pericarditis, and in 17 they were not suggestive of pericarditis. Table 3 summarizes the observations.

Elevation of RS-T Segments—Of the 53 cases of all types of pericarditis, there were elevations of the RS-T segment of 1 mm or more in one or more of the standard leads in 22 cases. In all but 2 instances these elevations were in cases of acute pericarditis. In 1 case hemopericardium was present, and in the other pericarditis,

TABLE 3—*Frequency Distribution of Cases of Pericarditis in Which Abnormal Electrocardiographic Patterns Were Observed in the Standard Leads**

	Frequency
Occurrence of elevation of RS-T segment	
In leads I, II and III	3
In leads I and II	9
In leads II and III	4
In lead I	4
In lead II	5
All types	22
Absence	31
Changes in the T waves	
In leads I, II and III	5
In leads I and II	6
In leads II and III	5
In lead I	5
Low voltage or isoelectric in leads I, II and III	13
Low voltage or isoelectric in leads I and II	3
Low voltage or isoelectric in leads II and III	1
Low voltage or isoelectric in lead I	9
Exaggerated upright T wave	8
Dome-like	12
Total number of cases in which the T wave was changed	47
Total number of cases in which the T wave was not changed	6
Changes in QRS voltage	
Low voltage present	20
Low voltage absent	33
Q ₁ and Q ₃ patterns	
A typical Q ₁ and Q ₃ pattern was not present in any of the cases. In 1 case a Q ₃ pattern was approximated	

* Since more than one abnormality may occur at different times in the same case, the sum of the number of cases in which different abnormalities of the RS-T and T wave patterns occurred is greater than the number of cases in which one abnormality of the RS-T and T waves occurred.

probably in the acute stage, though possibly subacute, existed without known effusion. Thus, in 20 of the 32 cases of acute pericarditis there was some elevation of the RS-T segment. Elevation of the RS-T segment in both leads I and II was the most frequent finding. The elevation was greatest in lead II in 10 cases.

The deviation in the RS-T segment which is most characteristic of pericarditis is the elevation in the three standard leads (fig. 6d). Frequently the RS-T segments in leads I and II are elevated, while

the segment remains isoelectric or is insignificantly elevated in lead III (figs 4c and 6b and c). Significant degrees of reciprocal depression of the RS-T segment in lead III usually observed in association with elevation of the segment in lead I in the T_1 pattern of infarction of the anterior apical portion of the left ventricle did not occur in our cases of pericarditis.

Although the contour of the RS-T segment characteristic of pericarditis is elevated, it is different from that of cardiac infarction. Since in the early stage of acute pericarditis the T wave may be upright and sometimes exaggerated, the RT segment is concave upward, as contrasted with the upward convexity of the RT segment in acute myocardial infarction (compare figure 6d with figure 5c). In other

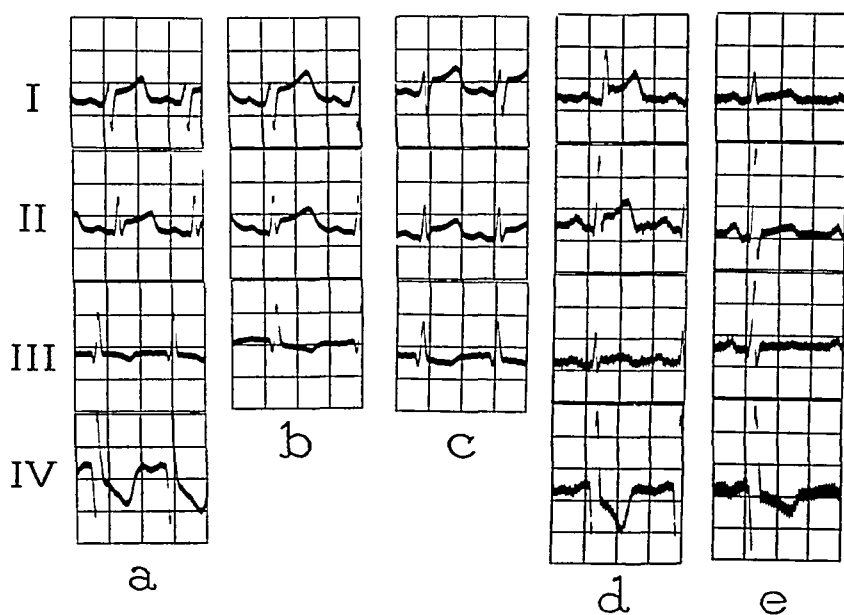


Fig 6—In a case of acute pericarditis with proved effusion a standard electrocardiogram and tracing from the fourth lead (a) were taken on October 30, before there was any evidence of pericardial effusion. Standard electrocardiograms (b and c) were taken on October 30 and 31, respectively, after pericardial paracentesis. Note (1) the elevation of the RS-T segments in the standard leads and depression of the RT segment in lead IV and (2) the upward concavity of the RS-T segments, ending in upright and exaggerated T waves, in leads I and II. This electrocardiogram is regarded as pathognomonic of pericarditis.

In a case of acute pericarditis without known effusion an electrocardiogram (d) was taken on January 26 and another (e) on January 30. There was never any evidence of pericardial effusion in this case, and the patient was dismissed from the hospital in good condition on February 6. Note the similarity of this electrocardiogram to that of the patient tracings for whom are shown in figure 6 a, b and c, and in whom pericardial effusion was known to be present. Note also the rapid reversion of the electrocardiographic pattern to normal without the development of negativity of the T wave.

instances it rises in a straight line as an inclined plane from its origin to end in an upright T wave, which may be exaggerated (fig 4c). In a third type the elevated RS-T segment may have a broad domelike shape with its convexity directed upward (fig 7). The elevation sometimes disappears after only a few days and is usually of shorter duration than in infarction. It may persist until the end of the third week but is rarely observed in cases of subacute or chronic pericarditis.

Changes in the T Wave—Changes in the T wave of some type were present in 47 of the 53 cases. All 6 cases in which there were no such changes were instances of the acute type.

Early in acute pericarditis the T wave is upright and frequently exaggerated (figs 4c and 6a, b, c and d). In 8 cases this change was shown. The T wave may then change to any position between this and

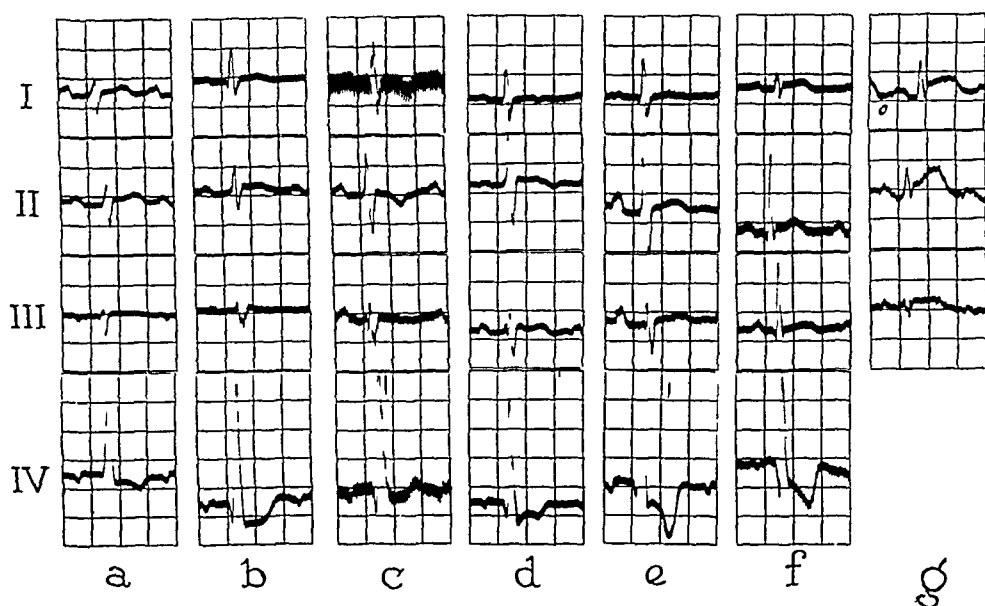


Fig 7—Electrocardiogram *a* was taken in a case of rheumatic pericarditis without known effusion. Other electrocardiograms were taken (*b*) on September 7, (*c*) on September 18 and (*d*) on October 12. Electrocardiogram *e* is that in a second case of pericarditis without known effusion. Electrocardiogram *f* was obtained in a third case of pericarditis without known effusion. Note the dome-shaped T waves in the standard leads in *a*, *b* and *e*. Attention is called to the evolution of the T waves in *b*, *c* and *d*. In *c*, T_1 has a "cove plane" contour and T_4 is positive, but Q_4 is normal, an important fact in the exclusion of acute or subacute infarction of the anterior portion of the left ventricle. Note the tendency of R- T_4 to be depressed in most of the tracings. Unless one is aware of the behavior of the fourth lead in pericarditis an unwarranted diagnosis of coronary occlusion may be made. An electrocardiogram (*g*) was obtained in a case of generalized pericarditis without effusion, and the diagnosis was confirmed at necropsy. A friction rub was never heard and the clinical diagnosis was based on the electrocardiogram. In this tracing the dome-shaped RS-T segments with upward convexity constitute a change sometimes observed in pericarditis (fig 5c).

the inverted form. The changes occur at varying rates, depending probably on the nature of the underlying pathologic process. There is also a variability in the extent of the changes in the T wave, since in some cases the T wave does not go through a stage of negativity but reverts to normal after a period during which it is flattened to a greater or lesser degree.

The stage of T waves of low voltage or of isoelectric T waves usually occupies a considerable period, and consequently it will be present in a large proportion of the tracings in certain individual cases as well as in a group of cases (fig 2*c* and *d*). This fact is exemplified by the presence of this form of the T wave in 26 of the cases of the present group, in one half of which it occurred in the three standard leads.

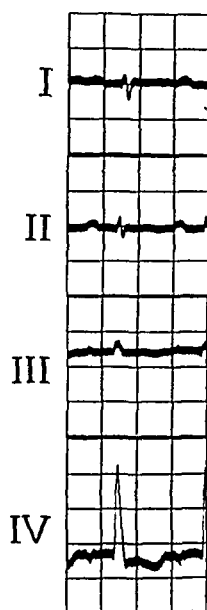


Fig 8—Electrocardiogram of a patient with exophthalmic goiter. Because of the low voltage of the QRS complex and T wave, pericarditis was suspected. A typical friction rub was heard first five days after this tracing was taken and was present for the succeeding fortnight. T waves of low voltage or isoelectric T waves in the standard leads with or without low voltage of the QRS complexes always suggest the involvement of the pericardium. Pericardial paracentesis yielded no evidence of pericardial effusion in this case. Note the absence of Q_4 , a phenomenon rarely observed in cases of pericarditis. There was no clinical evidence of coronary disease, and nothing in the history suggested coronary thrombosis.

T waves of low voltage in all the standard leads, with or without low voltage of the QRS complexes, are probably more frequently an indication of pericarditis than of any other single cardiac lesion (fig 8). The large proportion of cases of pericarditis in Master's report in which the condition was found to be associated with low voltage of the T

waves is another indication of the significance of this electrocardiographic abnormality. Frequently, when the T wave is of low voltage it may assume a characteristic domelike contour with a gradual slight rise, a flattened summit and a gradual fall (figs 2c and 7a, b and e). Inversion of the T wave in all three leads carries the strongest suggestion of pericarditis, but in our study there were an equal number of instances of its inversion in leads I and II, in leads II and III and in lead I alone.

Although the inversion of the T wave in pericarditis is similar in contour to the inversion in cardiac infarction, its depth is not as great as in some instances of infarction. Also inversion of the T wave does not occur in pericarditis while the RS-T segment is elevated, in contrast to the prevalence of this pattern in cases of infarction. In instances in which the T wave is inverted in lead I while it is upright in lead III there is a lack of the exaggerated positivity of the T wave in lead III which is seen in the pattern of the subacute stage of infarction of the anterior portion of the left ventricle. The reciprocal deviation of the RS-T segment observed in acute coronary thrombosis is lacking usually in pericarditis.

Voltage of the QRS Complex—A relation between the low voltage of the QRS complex in all the standard leads and the presence of a pericardial effusion was observed in 3 of the 5 cases of proved effusion and in 5 of the 9 cases of probable effusion. In the 3 cases of proved effusion in which there was low voltage of the QRS complex, the amounts of fluid observed by pericardial paracentesis were 250, 500 and 800 cc, respectively. In 1 of the 2 cases of proved effusion in which low voltage of the QRS complex was absent, 150 cc was found at necropsy and in the other 300 cc was obtained on pericardial paracentesis. Low voltage of the QRS complex in all three standard leads was observed in 5 of the 9 cases of calcification of the pericardium, in the case of chronic tuberculous pericarditis, in 3 cases in which there was known effusion and in 2 cases in which there was no effusion.

Electrocardiograms taken in 2 cases after pericardial paracentesis showed no significant changes in QRS voltage (fig 6a and b). In 1 case there was a slight decrease in voltage during the period when fluid was known to be accumulating. In several cases the voltage was lowest during the acute phase of the disease and increased appreciably during recovery.

Changes in the Q Wave—Although small Q waves were present in a number of cases, a Q_3 pattern was approximated only in a case in which there was an associated cardiac lesion of indeterminate type.

OBSERVATION IN THE PRECORDIAL LEAD AND COMPARISON WITH
THOSE OF THE STANDARD LEADS

Tracings from precordial leads were obtained in 17 cases. They seldom gave crucial diagnostic information of pericarditis which was not present in the standard leads. They were frequently within normal limits in the presence of definite changes shown by the standard leads.

Elevation of the RS-T Segment—There were 4 cases in which the RS-T segment was elevated in one or more of the standard leads and was isoelectric in the precordial lead. In all the 4 cases in which the RS-T segment in the precordial lead was abnormally depressed it was elevated in the standard leads (figs 6*a* and *d* and 7*b* and *f*).

Changes in the T Wave—The T wave in lead IV was upright in 6 cases. In 3 of these cases there were significant inversions of the T wave in the standard leads, and in 2 cases the T waves were of low voltage in all the standard leads. In 1 case there were only minor changes in the T wave in leads I, II and III, while T_4 was markedly upright. There were 3 cases in which the T wave in the precordial lead was diphasic or isoelectric. In all these cases there were significant changes in the T waves in the standard leads. In 8 cases there was shallow inversion of the T wave in the precordial lead, and in these cases there were significant changes in the T waves in the standard leads. There were 2 cases in which the T wave in lead IV was inverted and of normal depth, in both cases there were significant changes in the T wave in the standard leads. There were 2 cases in which the T wave in lead IV was exaggerated in depth. In both these cases the T wave in the standard leads was upright or exaggerated (fig 7*f*).

Q Wave—The Q wave in lead IV was absent in 1 case, that of a boy aged 15 with acute rheumatic fever (fig 7*a*). There were on record no electrocardiograms made before this attack or since his recovery.

Absence of the Q wave was noted in a number of the cases of chronic tuberculous pericarditis reported by Harvey and Whitehill¹⁸. In 1 case in our series and in 2 additional cases of pericarditis observed since the completion of this study the Q wave was absent in the Wolferth precordial lead. In 1 of the cases in which lead IV F was taken the R wave likewise was practically absent. It was hoped that the presence of a normal Q wave in the Wolferth lead in cases of pericarditis would be so constant as to be useful in excluding the occurrence of infarction of the anterior portion of the left ventricle as a possible cause of the electrocardiographic changes. In general our studies indicate that the Q wave in lead IV is infrequently absent in pericarditis. When it is absent the presence or absence of anterior infarction or its

conjoint existence with pericarditis will have to be determined by the presence or absence of Q_1 and T_1 patterns

COMMENT

Theoretic Conceptions of the Causation of the Electrocardiographic Pattern of Acute and Subacute Pericarditis—The work of Vander Veer and Norris and of Bellet and McMillan¹⁰ seems to indicate that the relation between the characteristic pattern of pericarditis and the presence of subepicardial myocarditis, observed experimentally by Fowler, Rathe and Smith⁷ and by Herrmann and Schwab,⁹ exists also in clinical instances of pericarditis. It has also been repeatedly demonstrated that the introduction of fluid under pressure into the pericardial cavity of animals produces changes in the RS-T segment of the electrocardiogram similar to those observed in clinical instances of pericarditis.

Whether or not pericardial effusions affect the electrocardiogram in clinical instances of pericarditis through a physiologic mechanism similar to that in these experiments is questionable. The experiments of Foulger and Foulger,⁶ mentioned previously, seem to us to be particularly significant in this connection. Their implications would greatly limit the frequency of occurrence of conditions in which this mechanism might conceivably be responsible for the electrocardiographic pattern. One might reasonably expect that this would occur in cases in which there is clinical evidence of cardiac tamponade, such as in cases of hemopericardium and massive purulent effusions. One might reasonably expect that it would not occur in cases in which cardiac tamponade is not present. Rheumatic pericarditis, in which electrocardiographic changes are frequently encountered, practically never leads to cardiac tamponade, and the amount of pericardial fluid in most cases of pericarditis due to varying factors is insufficient to produce cardiac tamponade.

The proof of this reasoning must come from a correlation of the clinical evidences of the presence or absence of fluid with the electrocardiographic pattern in cases of pericarditis. Also, the effect on the elevation of the RS-T segment of the removal of pericardial effusions gives information concerning the part played in the production of the electrocardiogram by the pressure of the fluid. Numerous examples of such observations have appeared in the literature, and there seems to be no constant relation in the majority of instances,³⁵ a fact verified by our own experience.

35 Holzmann, M. *Elektrokardiographische Befunde bei Perikarditis*, *Helvet med acta* **3** 249-257 (July) 1936. Vander Veer and Norris² Winternitz and Langendorf³ Bellet and McMillan¹⁰ Peel¹³ Schondorf¹⁴

Figure 6a shows well marked elevation of the RS-T segment in a case of pericarditis with purulent effusion. Removal of 250 cc of pus resulted in the heart sounds becoming clearer, but the electrocardiogram taken soon after (fig 6b) showed no lessening in elevation of the RS-T segment. Figure 3b shows well marked elevation of the RS-T segment in a case of pericarditis secondary to uremia in which necropsy a few days later did not show pericardial effusion. In 2 other cases in which there were no clinical signs of pericardial effusion, well marked elevation of the RS-T segment was present (figs 6d and 7g). In both these cases physical examination and cardiac roentgenograms revealed no evidence of pericardial effusion.

Factors Determining the Incidence of Electrocardiographic Changes of Diagnostic Value in Pericarditis—In the first few days after the onset of pericarditis the electrocardiogram usually shows elevation of the RS-T segment, which has an upward concavity of contour or is almost a straight line ascending at an angle to end in an upright, and at times an exaggerated, T wave. This observation, especially when it occurs in all three standard leads, is peculiarly characteristic of pericarditis and is therefore of great diagnostic value. Somewhat later, after the RS-T segment has returned to the isoelectric line, the series of changes in the contour and direction of the T waves appears. When all three standard leads are similarly involved, the electrocardiogram is characteristic. Otherwise, the evolution of the change in the T wave observed by taking repeated electrocardiograms provides much greater diagnostic aid than the pattern in a single tracing. There is no doubt that the electrocardiographic pattern of chronic pericarditis is frequently less characteristic than that of other stages of the disease. The tracing lacks the change in the RS-T segment seen in the acute stages. The inversion in the T wave is not characteristic. However, the pattern is remarkably uniform in the great majority of instances and is nearly always suggestive of pericardial involvement (fig 9). This suggestion is often of value in arousing one's suspicion that pericarditis is present and leads to further diagnostic procedures.

In rare instances many clinical features may point to the presence of pericarditis with effusion when the underlying lesion is actually severe myocardial damage with extreme cardiac dilatation. Two such instances were discovered in the review of the present series of cases. In both cases the cardiac silhouette on roentgenologic examination suggested a pericardial effusion. In both the diagnosis of pericarditis with effusion was made, and pericardial paracentesis was performed, with negative results. The ages of the patients were 18 and 35, respectively. Necropsy in the first case revealed marked myocardial fibrosis and ventricular dilatation, of indeterminate origin, in the second occlusion

of the left coronary artery with chronic infarction of the left ventricle and marked ventricular dilatation was observed. The pericardium was normal in both cases. The tracings in the first case (fig 10a) showed marked notching of the QRS complex in lead II and a prominent Q wave

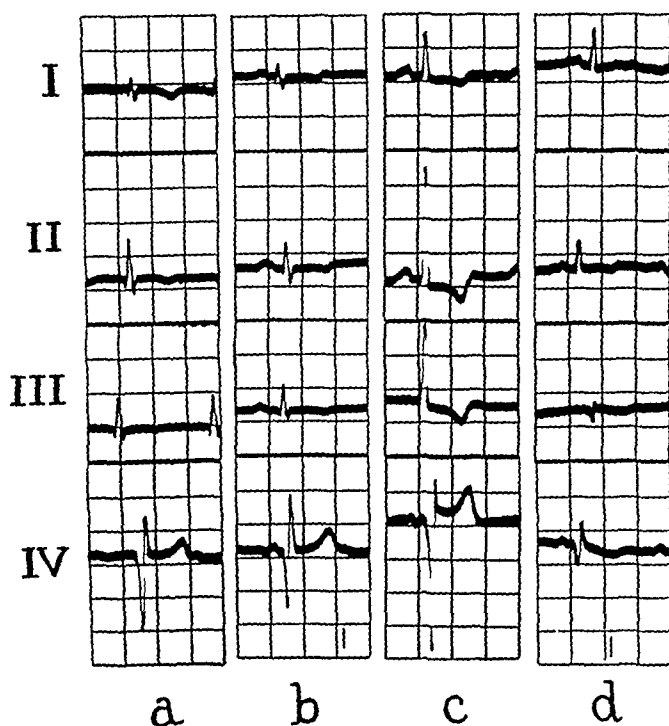


Fig 9—Standard electrocardiograms and tracings from the fourth lead in 4 cases of chronic constrictive pericarditis, with calcification proved at operation

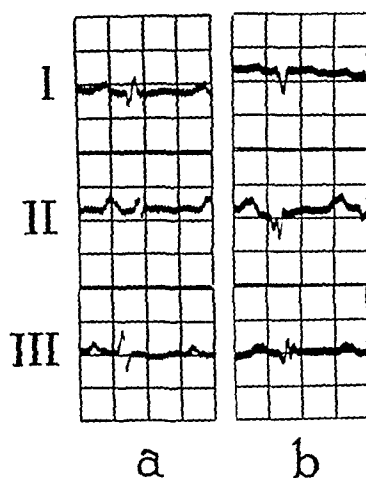


Fig 10—Electrocardiograms obtained in 2 cases of marked myocardial damage, in which the clinical pictures resembled pericarditis but in which the pericardium was proved normal at autopsy. The low voltage of the QRS complexes and of the T waves suggests pericarditis, but notching of the QRS complexes is important in avoiding such a conclusion

in lead I, in the second case (fig 10b) there were widening and marked notching of the QRS complex. The QRS complex in chronic peri-

carditis, though of low voltage, is nearly always free from widening and notching, and prominent Q waves are not seen. Thus, the electrocardiogram may be of aid in the differential diagnosis in cases in which other clinical data may be misleading.

In considering the grading of the diagnostic value of the electrocardiograms in the cases in the present study, we attempted to be conservative. The electrocardiograms classified as pathognomonic are illustrated in figures 6 and 7 *g*. Two of the three tracings in these 3 cases were obtained within the first two days following the onset of symptoms. The average number of tracings of each class obtained per patient was as follows: pathognomonic, 3.5, strongly suggestive, 5, suggestive, 1.8, and not suggestive, 1.2. The majority of the patients comprising this study were under observation during the period preceding the development of knowledge of this subject and therefore were not carefully studied cardiographically. The occurrence of pathognomonic tracings in 3 cases and of strongly suggestive tracings in 22 cases, making a combined total of nearly 50 per cent of the whole group, would seem under the circumstances a favorable comment on the frequency of the occurrence of electrocardiographic changes of diagnostic value. It is undoubtedly true that the opportunity to obtain tracings in the early stages of pericarditis and the ability to take serial tracings in the course of the disease will increase the frequency with which characteristic or diagnostic electrocardiograms are observed.

SUMMARY

In acute pericarditis the most characteristic electrocardiographic change consists in elevation of the RS-T segment and in exaggerated T waves in the standard leads. The RS-T segment may be elevated in all three leads, which constitutes the most characteristic picture, or in leads I and II, in leads II and III or in lead I alone. Reciprocal depression of RS-T₃ when RS-T₁ is elevated and depression of RS-T₁ when RS-T₃ is elevated are rarely observed, and this characteristic serves to distinguish these changes from those observed after acute myocardial infarction. In acute pericarditis the ascending limb of the elevated RS-T segment is concave or ascends as a straight line of an upward inclined plane, in contrast to the convex contour of this limb seen frequently in tracings in cases of acute myocardial infarction. In the early stage the T waves may be exaggerated and rather sharp (fig 4*c*), or they may have a dome-shaped summit (fig 7*g*).

The elevation of the RS-T segment in acute pericarditis is apt to be transitory, certainly more so on the average than the elevation observed after acute myocardial infarction. In the subacute stage of pericarditis the elevations disappear, and the standard leads may return to normal.

or be followed by T waves of low voltage, by dome-shaped or isoelectric T waves or by actual negativity of the T waves. Negativity or low voltage of the T waves in all the standard leads constitutes the most suggestive picture of pericarditis at this stage. The T wave, if inverted, may have a contour closely resembling the "cove plane" T wave observed in the stage of healing of myocardial infarction, though frequently it lacks the depth of the T wave commonly observed in the latter condition.

Elevation of the RS-T segments and exaggerated T waves in the standard leads can be produced by a rapidly accumulating effusion, but effusion is not essential in the production of such changes.

The presence of pericarditis complicating coronary occlusion will be signalized chiefly by elevation of the RS-T segments in the three standard leads or in leads I and II, with little or no elevation but with absence of reciprocal depression of the segment in lead III. If this pattern is succeeded by negativity of the T waves in all the standard leads, the evidence for pericarditis complicating coronary occlusion is greatly strengthened. It is probable that pericarditis complicating acute infarction of the posterior portion of the left ventricle will cause elevation of RT_1 or prevent the depression of ST_1 , normally anticipated in this condition. Pericarditis complicating acute myocardial infarction frequently interferes with the development of T_1 and T_3 patterns. However, Q_1 and Q_3 patterns may be present to indicate the site of infarction and to suggest that pericarditis alone is not responsible for the electrocardiographic changes. Absence of a Q wave in the Wolfersith lead and of an R wave in lead IV suggests, but does not denote positively, that acute infarction of the anterior portion of the left ventricle has occurred.

In tuberculous pericarditis we have not observed the elevation of the RS-T segment, though it is conceivable that it might occur in an acute stage. The changes observed in this condition are chiefly those observed in chronic constrictive pericarditis.

The electrocardiographic changes observed in chronic constrictive pericarditis and at certain stages of healing in acute pericarditis in some patients include (1) low voltage of the QRS complexes in all the standard leads, (2) low voltage of the T waves in all standard leads or, in the most characteristic instances, inversion of the T waves in all standard leads and (3) dome-shaped, flattened, isoelectric or negative T waves in one or more standard leads (fig. 9).

Typical Q_1 or Q_3 patterns have not occurred in our series of cases of pericarditis unassociated with acute myocardial infarction.

The precordial lead may or may not exhibit significant changes. The chief changes observed are reversal of the normal direction of or shallowness of the T wave. In acute pericarditis there is a tendency to depression of the RT segment in the Wolfersith lead, though it may be absent when elevations of the RS-T segment are present in the standard leads.

In most instances the Q wave is preserved in a normal form, an observation which is of considerable value in excluding the occurrence of acute infarction of the anterior portion of the left ventricle

Unless tracings are taken within two or three days after the onset of acute pericarditis, diagnostic electrocardiographic changes may be missed. Serial tracings taken over a period of days, or even weeks, may be required to differentiate the tracings of pericarditis from those of acute myocardial infarction. A rapid return to normal is often sufficient to exclude the latter condition.

Considerable experience and detailed knowledge may be required to recognize the electrocardiographic evidences of pericarditis. Occasionally they are diagnostic. Frequently they are suggestive and direct clinical studies toward the proper diagnosis. They must be correlated with the clinical picture and observations to serve their greatest usefulness. Familiarity with the changes is essential if confusion with other cardiac lesions is to be avoided. Pericarditis is much more frequent than is suspected, its recognition is often difficult but is highly important, and a proper understanding of the electrocardiographic changes produced by it will result in a great increase in the proportion of cases recognized in medical diagnosis.

PURE MITRAL STENOSIS IN YOUNG PERSONS

BERNARD J WALSH, M D

EDWARD F BLAND, M D

AND

T DUCKETT JONES, M D

BOSTON

A comprehensive study of more than 1,700 children and adolescents with rheumatic fever has been in progress since 1920 at the House of the Good Samaritan in Boston. This large group includes 81 patients who have acquired the physical signs of so-called pure mitral stenosis.

These physical signs consist of (1) a low-pitched (often coarse) murmur at or near the cardiac apex, which begins in mid or late diastole and ends with crescendo in (2) an abrupt, slapping first sound. A corresponding thrill and shock are commonly associated with the more advanced lesions, and accentuation of the pulmonary second sound is usually present. For our purpose in this special study we have excluded a considerable number of patients with undoubted mitral stenosis who, in addition to the physical signs mentioned, had a blowing systolic murmur at the cardiac apex, characteristic of associated mitral regurgitation. We realize that in many of these patients (especially when the diastolic murmur is prominent and the systolic murmur is minimal) the clinical distinction between "pure" stenosis and a combined form of deformity of the mitral valve may be artificial. However, it has seemed best to confine our present observations to the group with uncomplicated mitral stenosis. Furthermore, we have excluded those patients (relatively few) in whom signs of free aortic regurgitation developed concurrently with their mitral valve deformity, to avoid the possibility of error in interpreting the apical diastolic murmur present in some as due to mitral stenosis, whereas actually in a few instances it may have been an Austin Flint phenomenon. We have, however, retained in this special group with "pure" mitral stenosis 19 patients who from the onset had evidence of slight involvement (regurgitation) of the aortic valve, manifested by a soft blowing murmur early in diastole at the base of the heart, as well as 34 additional patients in whom this sign appeared later. Whether or not this may represent,

From the House of the Good Samaritan

The expenses of this study have been defrayed by a grant from the Commonwealth Fund

in an occasional instance, slight functional insufficiency of the pulmonary valve (Graham Steell murmur) rather than of the aortic valve is here of academic interest. We believe that such an interpretation is rarely justified, and then only in the presence of strongly supporting collateral evidence in the pulmonary circuit as well as in the heart. Auricular fibrillation, not present in any of the patients when mitral stenosis was first established, developed later in 3.

This special group of patients with pure mitral stenosis is of interest primarily because of (1) the observed evolution of the physical signs in the heart and (2) the manifestations of the rheumatic fever in these persons, which have been sufficiently unusual to suggest that a rather characteristic form of the disease favors the later development of this particular deformity in young people. Furthermore, it throws additional light on certain clinical features of mitral stenosis in adult patients. The average age at which the initial rheumatic fever began in this special group was 9.3 years, which closely approximates the age of onset in our larger series of 1,700 patients. No patient beyond 21 years of age at the onset of the rheumatic fever has been included.

DEVELOPMENT OF PURE MITRAL STENOSIS

The changing physical signs in the heart prior to the stage of pure mitral stenosis have been observed in 48 of the patients in our group. In the remaining 33 patients the signs were already established when the patients were first seen by us.

In table 1 we have arranged the 48 patients with the observed evolution of physical signs into two subgroups, according to the presence or the absence of demonstrable cardiac involvement with the initial rheumatic fever. The majority (27 patients) had auscultatory signs of valvular disease from the onset, consisting of (1) a loud, blowing systolic murmur at the cardiac apex (mitral regurgitation), in 5 instances, (2) a loud systolic murmur and a poorly defined diastolic rumble at the apex (involvement of the mitral valve—mitral regurgitation and questionable stenosis), in 15 instances, (3) a short, low-pitched diastolic murmur after the third heart sound at the apex, without crescendo or accentuation of the first sound and without an accompanying systolic blow (involvement of the mitral valve—questionable stenosis), in 4 instances, (4) a slight diastolic blow after the second sound at the base of the heart, usually best heard to the left of the upper portion of the sternum and unassociated with murmurs at the cardiac apex (slight aortic regurgitation), in 3 instances. A similar murmur was present in 53 of the 81 patients in our series, in addition to the signs of involvement of the mitral valve already noted.

The second subgroup (table 1) consists of the 21 patients who on recovery from their initial rheumatic fever had no clinical evidence of cardiac involvement—so-called potential rheumatic heart disease. The subsequent appearance and the later progression of the physical signs in the heart prior to the establishment of pure mitral stenosis are best displayed by this relatively small, but closely followed, group. The first evidence to appear in 2 of these patients was a systolic murmur at the cardiac apex consistent with mitral regurgitation. This, in turn, slowly progressed to the next stage, represented by the apical systolic and diastolic murmurs of mitral regurgitation and stenosis. In 3 additional patients the latter combination appeared directly as the first indication of heart disease. Later, over a period of years, the systolic murmur gradually became less loud, and ultimately it disappeared as the diastolic

TABLE 1—*Development of Pure Mitral Stenosis (48 Patients)*

Original Status		Number of Patients				
		Period from Onset of Rheumatic Fever to Established Mitral Stenosis (Years)				
		1-5	6-10	11-15	16-20	20-24
Group 1	Rheumatic heart disease	27				
	(1) Mitral involvement (regurgitation)	5	1	2	1	1
	(2) Mitral involvement (regurgitation and ? stenosis)	15	1	10	3	1
	(3) Mitral involvement (? stenosis)	4	1	1		1
	(4) Aortic regurgitation (slight)	3	1	2		
Group 2	Potential rheumatic heart disease	21	2	13	2	4
Totals		48	5	27	8	2

murmur and first heart sound acquired the characteristics of pure stenosis. In contrast to this sequence of events, the earliest physical sign to appear in the remaining 16 patients (75 per cent) was a short mid-diastolic murmur, following a rather prominent third sound, at the apex of the heart. This slight apical diastolic murmur slowly evolved into the characteristic crescendo presystolic murmur of mitral stenosis, without the occurrence at any stage of a systolic murmur. We suspect that the absence of significant enlargement of the heart during the years after the initial rheumatic fever is primarily responsible for the absence of an associated systolic murmur. Minimal involvement of the aortic valve (slight regurgitation) became manifest at the same time in 8 patients, and in 1 instance it preceded by several months the appearance of the mitral diastolic murmur.

It is to be further noted from table 1 that in relatively few instances (5 patients) did pure mitral stenosis become established in the first five year period. The earliest occurrence was three years after the initial attack of rheumatic fever. In the majority of the patients (27) it devel-

oped during the second five year period, but there remained a considerable number (14) in whom the characteristic signs did not become established until the third five year period after their original rheumatic fever. In 2 patients of this series pure mitral stenosis was established more than twenty years after their original illness. These clinical observations are in close agreement with previously recorded postmortem studies,¹ in which it was shown that the ultimate development of extensive valvular deformity of the mitral orifice (either with or without actual stenosis) probably requires a minimum of two years, and in most instances a considerably longer period.

SPECIAL FEATURES OF THE RHEUMATIC FEVER

Rheumatic fever in this group of 81 patients has been characterized by a mild course. The evidence for this conclusion is based on three important aspects of the disease: (1) the actual clinical manifestations of rheumatic fever, (2) the incidence and degree of the initial involvement of the heart, and (3) the subsequent complications.

TABLE 2—*Relative Severity of Rheumatic Fever (81 Patients)*

	Number of Patients	
	Initial Attack	Later Recurrences
Chorea (uncomplicated)	17	12
Rheumatic fever (mild)	63*	49
Rheumatic fever (severe)	1	8
Total	81	69

* No recognizable illness, 4, poor health, 13 poor health plus joint pains or chorea, 46

Clinical Manifestations—An appraisal of the relative severity of rheumatic fever as regards both the first attack and later recurrences is summarized in table 2. For the purpose of this appraisal we considered one or more of the following clinical signs to be indicative of a relatively severe form of rheumatic fever: subcutaneous nodules, exsanguinating nosebleeds, pericardial friction rub, pulmonary or pleural involvement, severe febrile episodes or congestive heart failure. The initial illness was manifested by uncomplicated chorea in 17 patients. This so-called pure chorea is considered by us a manifestation of mild rheumatic fever.² The remaining 64 patients (with 1 exception) were also considered to have a mild form of rheumatic fever, on the basis of the absence of a recognizable illness prior to the appearance of heart disease.

1 Bland, E. F., White, P. D., and Jones, T. D. The Development of Mitral Stenosis in Young People, *Am Heart J* **10** 995 (Dec) 1935.

2 Jones, T. D., and Bland, E. F. Clinical Significance of Chorea as a Manifestation of Rheumatic Fever, *J A M A* **105** 571 (Aug 24) 1935.

in 4, a period of poor health of obscure nature immediately preceding the appearance of heart disease in 13 and, in addition to poor health, either characteristic joint pains or chorea in the remainder (46). There was only 1 patient whose initial illness was considered to be severe by the foregoing criteria.

Recrudescences occurred in 69 (85 per cent) of the 81 patients. In the majority the later rheumatic manifestations were similar to those of the original attack, except that in 8 instances the subsequent clinical signs indicated a more severe form of the disease than had been present at the onset.

Involvement of the Heart—The extent of cardiac involvement, as shown by the size of the heart, is probably the most reliable index of the relative severity of rheumatic fever in childhood. In general, both the

TABLE 3—*Change in Size of the Heart (81 Patients)*

Original Status of Patients	Number of Patients							
	Original Size of Heart				Present Size of Heart*			
	Enlarged				Enlarged			
	Mod				Mod			
	Normal	Slight	erate	Marked	Normal	Slight	erate	Marked
Potential rheumatic heart disease	21				10	11		
Rheumatic heart disease								
1 Mitral involvement (regurgitation)	4	1			2	2	1	
2 Mitral involvement (regurgitation and ? stenosis)	12	3			10	4	1	
3 Mitral involvement (? stenosis)	3	1			2	2		
4 Aortic regurgitation (slight)	2	1			2	1		
5 Mitral involvement (established stenosis)	17	12	3	1	8	15	9	1
Totals	59	18	3	1	34	35	11	1

* Prior to final fatal illness in 11 cases

incidence of involvement and the degree of enlargement (dilatation) parallel the severity of the clinical manifestations of the disease, occasionally notable exceptions are encountered.

In table 3 is shown the distribution of the patients according to the size of the heart, both at the time of the original illness and after the development of pure mitral stenosis. It is to be noted, first, that recognizable involvement was present with the initial attack of rheumatic fever in only 57 per cent (60) of the patients, whereas our experience with the larger group of 1,700 patients indicates an initial involvement of the heart in approximately 70 per cent. Second, and perhaps of more importance, are the data for the size of the heart, both at the onset and during the subsequent course of the disease. The high percentage (73 per cent) of patients with no initial enlargement and the infrequency of even a moderate degree of enlargement for the remainder are striking.

The subsequent failure of the heart to enlarge significantly in the majority of the patients, in the presence of both recurring infection and developing stenosis, is an additional and important indication of the relative mildness of rheumatic fever

Subsequent Complications—To date, the subsequent course has been favorable for the majority of these patients, as reflected by the relative mildness of their recurrent rheumatism, the failure of the heart to enlarge significantly, the maintenance of an excellent functional reserve and the relative freedom from serious complications. Of the total group of 81 patients, 53 (65 per cent) are leading normal lives, while 13 (16 per cent) are slightly limited and 4 (5 per cent) are moderately limited by dyspnea on exertion. The remaining 11 patients (13 per cent) have died. This is in striking contrast to a death rate of approximately 24 per cent for a control group of 1,000 young rheumatic patients, of essentially the same age, followed for a comparable length of time (ten years).

Of the 11 deaths, rheumatic fever (and heart failure) was responsible for 5, pulmonary embolism (questionable acute pulmonary edema) for 2 and postoperative heart failure and bronchopneumonia for 1 each, and in 2 instances the cause of death could not be ascertained. Two patients were examined post mortem. In both instances the clinical diagnosis of marked mitral stenosis and slight aortic regurgitation was confirmed. In each the deformity of the mitral valve was found to be of the "fish mouth" type. Of the more or less special complications frequently associated with mitral stenosis in older patients, the following have occurred: hemoptysis in 8 patients, pulmonary embolism (questionable acute pulmonary edema) in 3, cerebral embolism in 1 and auricular fibrillation in 3. It is of interest that subacute bacterial endocarditis has not developed in any patient.

OTHER CONSIDERATIONS

In this report we have been concerned entirely with a group of young people in whom pure mitral stenosis has developed at an early age. It is well known that in many older patients this particular structural deformity may appear insidiously and remain clinically silent for years. In fact, if the disease is not discovered accidentally, the later occurrence of characteristic complications often directs attention for the first time to the heart. It is largely the occurrence of these special complications which may seriously impair the future health of the person. We refer to the ultimate appearance of auricular fibrillation in many patients. Less often the occurrence of hemoptysis, pulmonary infarction, acute pulmonary edema or peripheral embolism leads to the discovery of previously unsuspected mitral stenosis. Furthermore, one is often

impressed by the prominence of the signs of valvular deformity (stenosis) in older patients, which are out of proportion either to the degree of cardiac enlargement or to the impairment of cardiac reserve.

In the light of our present observations on younger patients in whom this deformity has developed as a result of mild rheumatic fever, the unusually high percentage of older patients with a "negative" rheumatic history is more readily understood. In fact, even in some of the younger patients who were under close observation at the time of their active disease it has been impossible to identify clearly as rheumatic fever their mild illness prior to the appearance of characteristic signs in the heart. It is probable that the favorable course of the illness in the majority of these patients (both young and old) is to be accounted for by the mild rheumatic fever, which in turn favors the continued integrity of the myocardium.

CONCLUSIONS

From a clinical study of 81 young patients who have acquired the physical signs of so-called pure mitral stenosis it has been shown that

- 1 The evolution of the physical signs prior to the establishment of this deformity required in the majority from five to fifteen years.

- 2 A relatively mild form of rheumatic fever appears to favor the development of this particular lesion.

- 3 The prolonged course of the disease in most patients with this deformity is fundamentally dependent on a benign type of rheumatic fever.

AN ACOUSTICAL STUDY OF THE STETHOSCOPE

FRANKLIN D JOHNSTON, M D

AND

EDWARD M KLINE, M D

ANN ARBOR, MICH

Although stethoscopes have been used since the time of Laennec, little exact information concerning the efficiency of different types is available, and apparently most physicians are influenced in their choice of a stethoscope by exterior finish or by features which make the instrument easy to use or convenient to carry rather than by its inherent worth as an acoustic instrument. Many different end pieces of the chamber and bell type are in use, and, although it is unlikely that all of these are equally satisfactory, little information is available as to the acoustic properties of the different kinds. The same may be said of the different arrangements of tubing that are employed. The tubes, usually made of rubber, may be long or short and of large or small diameter, and they may consist of soft gum rubber or of much stiffer material, but again few data concerned with their acoustic performance can be found. The purpose of this paper is to present the results of tests that have been carried out with an acoustic model in an attempt to answer some of the questions raised by lack of adequate studies of these problems.

The stethoscope in use is but one part of an acoustic system made up of (1) a source producing vibrations within the body which are transmitted through tissues, relatively dense as compared with air, to the wall of the chest, (2) the stethoscope, which receives the vibrations at the surface of the skin and transmits them to the ear, and (3) the ear itself, which permits one to hear the vibrations as sounds. This is not the place for a detailed discussion of the nature of the acoustic combination involved, but it should be emphasized that transmission takes place in two different mediums, one dense and the other rare, that the transfer of vibratory energy from one such medium to the

From the Department of Internal Medicine, University of Michigan Medical School

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other may occur with extremely low efficiency and that one function of the stethoscope is to increase materially the amount of sound energy that becomes available for auscultation. A more complete presentation of these matters will appear in another place.

METHODS

It is apparent, from the considerations mentioned, that experiments devised to determine how well different stethoscopes transmit sounds should be arranged so that the instruments are tested in a system of the same type as that in which they function when in actual use. For this reason the setup shown in figure 1 *A* was employed. A special telephone receiver (fig 1 *B*) driven by a variable frequency oscillator was placed within the heart of a cadaver by means of an abdominal-diaphragmatic approach so that vibrations of any desired amplitude and pitch were transmitted to the intact thoracic wall over the heart. The vibrations were picked up by the end pieces of the stethoscope and conveyed through the columns of air of the instrument to a condenser microphone. The output from the microphone was passed into a suitable vacuum tube amplifier and thence to an output meter of the rectifier type. The readings of this meter were proportional to the intensity of the sound waves striking the diaphragm of the condenser microphone. All tests were made with the end pieces of the stethoscope held rigidly against the same point on the precordium (fig 1 *C*), and great care was taken to be sure that each end piece was in air-tight contact with the skin.

Before any tests on stethoscope units were undertaken, attempts were made to standardize the vibrations transmitted to the wall of the chest so that their amplitude would be constant over the entire range of frequencies to be employed. This problem proved to be difficult and was not solved to our complete satisfaction. We finally used a crystal vibration pick-up, fixed at the chosen point on the precordium, and determined the value of the resistance (R , fig 1 *A*) which would give the same response on the output meter at each frequency. The condenser microphone and its associated amplifier were, of course, not in the circuit while these preliminary calibrations were being made.

The tests on stethoscopes were carried out in two separate studies. In the first group, a large number of different end pieces (fig 1 *D, E*) were used, while the rubber tubing was not changed. Tubes (fig 1 *F*) 47.4 cm in length, made of no. 1 tubing, which had an outside diameter of 11 mm and an inside diameter of 4 mm arranged as shown in unit 5 of figure 1 *E*, were employed for this work. In the second group of tests, on the other hand, the same end piece, no. 2, was used throughout, and the response of this bell with various lengths of the different tubes (fig 1 *F*) was determined.

The method of obtaining the data for each combination was as follows. After the desired tubing was placed on the metal binaural parts and the end piece had been satisfactorily approximated to the thoracic wall, the oscillator was set to deliver the lowest frequency that was used. The variable resistance (R) was then set to the value determined by the preliminary calibration previously mentioned and finally the reading of the output meter was recorded. The oscillator was then reset to the next higher frequency, and the process was repeated. The frequency run on a single unit was finished when the responses for eighteen different frequencies, from 20 to 800 cycles per second, had been determined. In all instances

the accuracy of the measurements was checked by redetermining the reading of the output meter for several different frequencies. The pitch of the sounds employed was known quite exactly, since the oscillator used was a General Radio Company type 613-B beat frequency oscillator, and its output was frequently checked on a cathode ray oscillograph by comparison with a 60 cycle wave

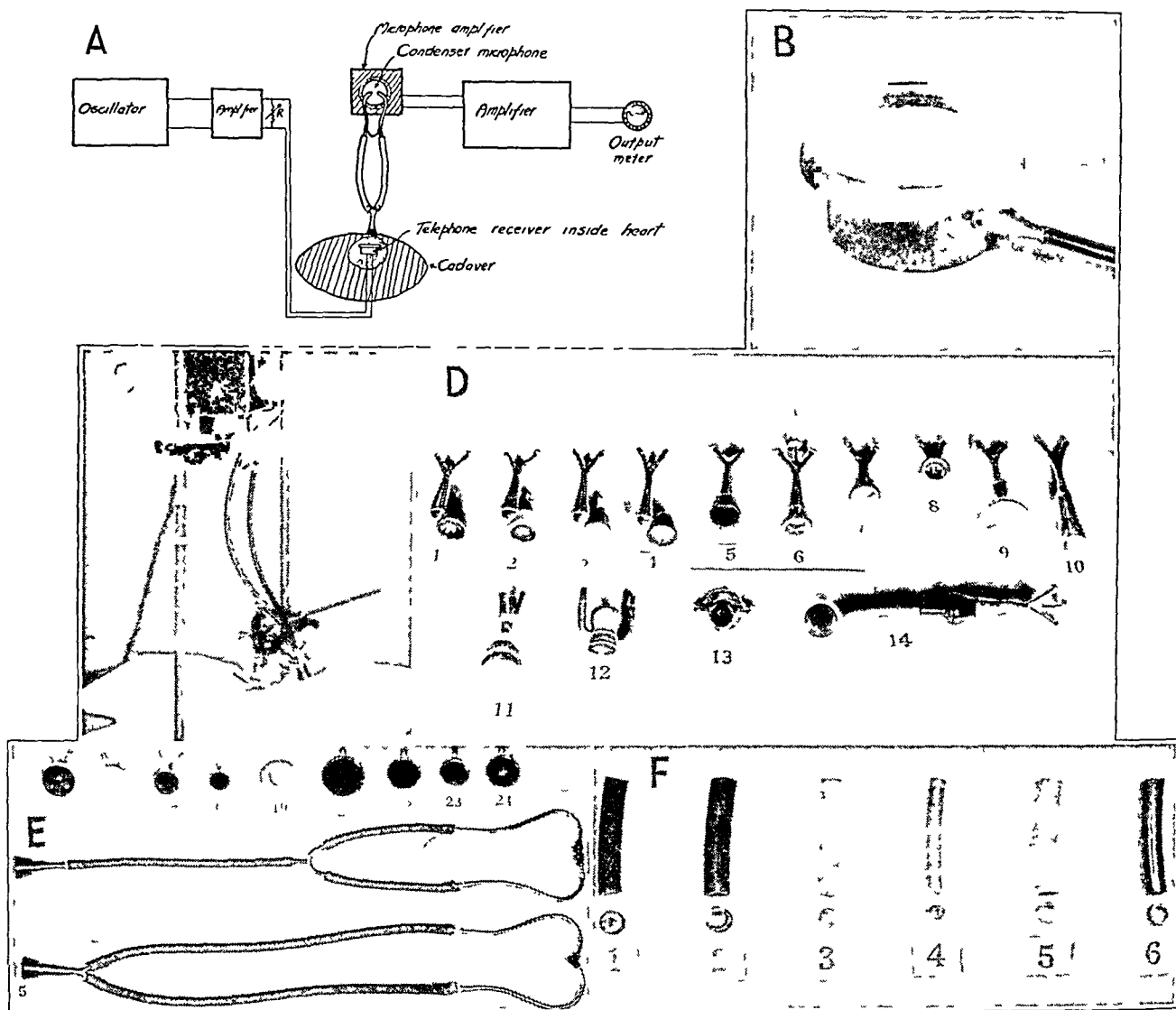


Fig 1—*A*, schematic diagram of setup employed *B*, special telephone receiver placed inside the heart *C*, the condenser microphone and arrangements for holding end pieces rigidly to thoracic wall *D* and *E*, different end pieces tested *F*, different kinds of tubing tested

RESULTS

The graphic method is the best and most concise way to present the large number of observations made in this study, and the performances of different units are plotted as curves in the charts reproduced. In all of them the frequency is plotted on the horizontal axis. In the first

chart (fig 2A) the readings of the output meter are plotted directly as the ordinates, but in the remaining charts the responses of the units in question are expressed as the logarithm of the ratio between the meter reading for the unit under test and that for a standard or reference combination. The actual calculations were made using the equation decibels (db) $= 20 \log_{10} \frac{p_1}{p_0}$, in which p_1 is the reading of the output meter for the unit under test and p_0 that for the standard unit.

The logarithmic or decibel scale has several important advantages. In the first place, by its use the performances of a large number of different end pieces or of different tubings with the same end piece are compared with the response of a single standard combination, and by this means variations in the response curves due to faulty calibration of the vibrations at the surface of the chest are in a large measure eliminated. As the standard unit we arbitrarily selected bell no. 1, or bell no. 1 with a rubber nipple (unit 2), and no. 1 tubing throughout, and in the charts its response is assumed to be 0 decibels over the entire frequency range. If the unit under test is superior to the standard the curve lies in the positive decibel region, above the 0 axis, while if the unit transmits certain sounds less well than the standard the line will be found in the negative decibel portion of the graph, below the 0 axis.

Since the loudness of sounds is proportional to the logarithm of the readings of the output meter and not to the readings themselves, the curves plotted according to the decibel system may be interpreted directly in terms of the sensation produced. It happens that a change of 1 decibel, plus or minus, represents approximately the minimal change in loudness that the human ear can perceive. In this work, however, we shall not consider that any unit under test deviates significantly from the standard unless its response curve lies 3 decibels or more above or below the 0 line.

Since the charts are self explanatory, it is not necessary to discuss in detail the results obtained with all the combinations tested, nevertheless, several of the most significant findings deserve particular emphasis. Charts A, B, D, E and H in figure 2 and F in figure 3 illustrate the improvement in transmission that results when a soft rubber nipple is placed over the end of an end piece¹ of the bell type

¹ Several observers (Oden, C. L. A. Soft Rubber Tip for the Bell Type of Stethoscope, *J. A. M. A.* **77** 623 [Aug. 20] 1921. Gordon, B. J. Lab. & Clin. Med. **14** 1111 [Aug.] 1929. King, G. C. Simple Stethoscope Tip, *J. A. M. A.* **97** 24 [July 4] 1931. Harrop, L. L. California & West Med. **43** 363 [Nov.] 1935) have suggested the use of a rubber nipple over the end piece to make the unit warmer and thus more agreeable for the patient, and also to reduce interference due to adventitious sounds, but, as far as we know, the nipple has not been used to improve the acoustic performance of the end piece.

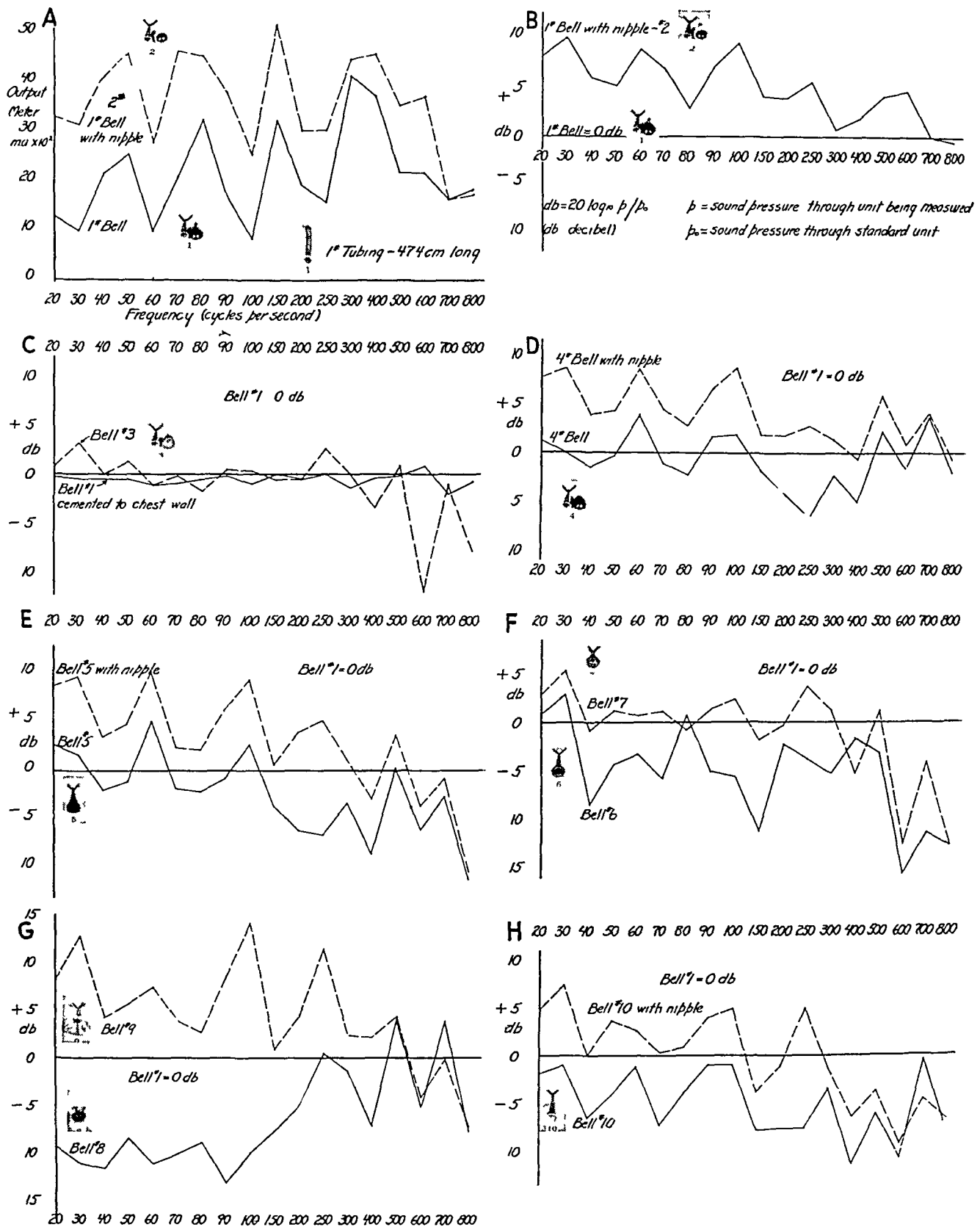


Fig 2—The results of tests with various end pieces of the bell type

(unit 2, fig 1 *D*) It will be observed that except at the higher frequencies the use of the nipple results in a significant gain in the response of the unit. The explanation for this finding is not clear, but a calculation shows that the slightly increased area of contact with the wall of the chest occasioned by the addition of the nipple is not sufficient to explain it, moreover, it is not due to the presence of a more perfect contact with the chest, for a test with bell no 1 after it had been securely fastened to the wall of the chest with rubber cement, as shown by the solid line in figure 2 *C*, yielded results practically identical with those obtained before the cement was applied.

The relative performance of several commonly used end bells is shown in charts *C*, *D* and *E* in figure 2. The solid line in the chart last mentioned shows that bell no 5, which has a large conical air chamber, compares favorably with bell no 1, which has a shallow chamber, up through a frequency of 100 cycles per second, but that for sounds of higher pitch its response falls off somewhat. Bell no 3 is identical with bell no 1 except that its lower part is made of soft rubber, and it is seen to respond much like the standard bell (line of dashes, fig 2 *C*) except for a distinct decrease in transmission for the highest frequencies. Bell no 4 is similar to bell no 1 except that in the former the small hole does not extend up as far into the metal frame as it does in the latter, and its behavior is similar to that of the standard unit except for a drop in transmission for frequencies between 150 and 500 cycles per second.

Figure 3 *C* gives the response curves for the large Bowles end piece with the regular stiff diaphragm (solid line), with a piece of 100 milligram film as a diaphragm (line of dashes) and, finally, without a diaphragm (dotted line). The stiff diaphragm obviously acts as a filter, causing considerable attenuation of the low-pitched sounds, while the higher frequencies, 150 cycles and above, pass easily. The flexible diaphragm does not have this property, for the curve obtained when the 100 milligram film was used and that obtained when no membrane at all was employed follow each other closely. The curves in figure 3 *D* show that a soft rubber sheath placed over the aperture of a large Bowles unit materially improves its transmission, and this is true whether a diaphragm is used or not. This result is rather surprising, and we are not able to give an adequate explanation.

Charts *F* and *G* in figure 3 show data on the performance of the Becton-Dickinson stethoscope units. The bells employed were similar in design to units 4 and 5, but the Bowles end pieces differed somewhat from the conventional pattern, and the connection with the end piece was made by a single rubber tube, with the division into two tubes occurring close to the metal binaural (unit 20, fig 1 *E*). The standard unit with which the Becton-Dickinson units were compared was bell

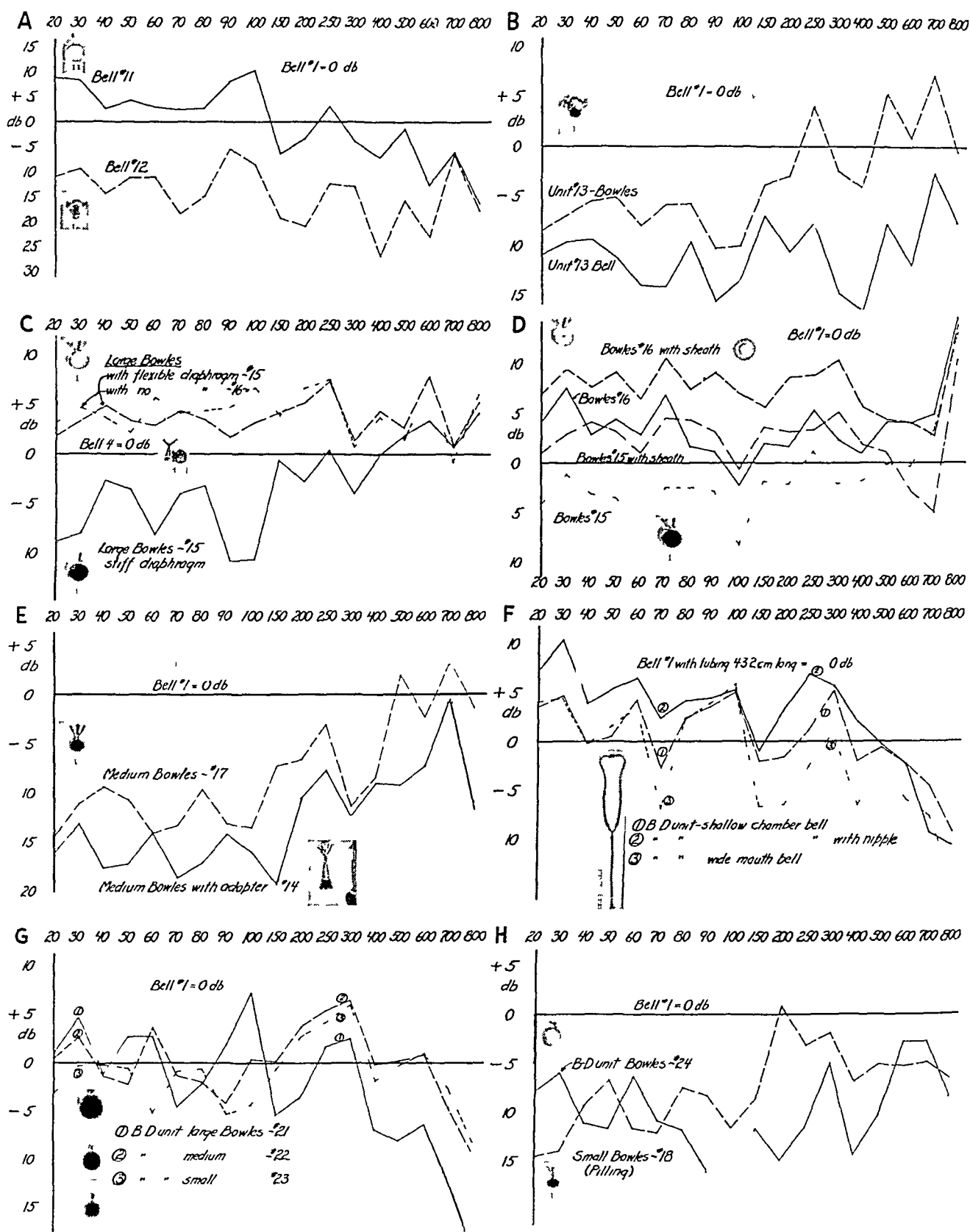


Fig 3—The results of tests on different end pieces, including unusual units of the bell type, conventional Bowles end pieces and Becton-Dickinson combinations

no 1 with no 1 tubing of the same over-all length as that used in the Becton-Dickinson stethoscope Chart *F* (fig 3) shows that the response for the shallow bell (curve 1) is slightly better than that for the standard, that the use of a rubber nipple (curve 2) further improves its performance and that the wide-mouthed bell with a large conical chamber, like that of unit 5, displays a significant drop in transmission at high frequencies Chart *G* shows that the Becton-Dickinson units with shallow chambers do not perform like the usual Bowles end piece with a stiff diaphragm They apparently do not attenuate the sounds of low frequency but show a fairly uniform response except that the sounds of high pitch are poorly transmitted

The performances of different kinds of rubber tubing and different lengths of tubing are shown in the charts of figure 4 The same end piece (bell no 1, with nipple, unit 2) was used throughout this work, and 40 cm lengths of no 1 tubing were used as the standard The four curves in figure 4 *A* give the relative responses of lengths of no 1 tubing varying from 70 to 15 cm It will be seen that the behaviors of all these tubes are roughly similar up to a frequency of 100 cycles per second At about this frequency more marked differences in response, due to resonance phenomena in the tubes, appear For example, the long 70 cm tubes have their first resonance peak at a frequency of approximately 100 cycles, with secondary peaks at higher frequencies, while the 15 cm tubes show resonance first at about 200 cycles The resonance phenomena are more clearly shown when the readings of the output meter are plotted directly, and in such graphs (not shown here) the first resonance peaks for tubes 30, 40 and 50 cm long lie between the maximum for the 15 and that for the 70 cm tubes, and secondary peaks are seen in their proper positions at higher frequencies

When the tests on tubing were undertaken, we expected to find that, except for resonance peaks, the transmission through long tubes would be considerably poorer than that through short ones because of loss in energy due to absorption in the rubber walls of the tubes It is apparent that this is not the case and that there is no decrease in response until the highest frequencies are reached

In figure 4 *B* the performance of no 2 tubing 20, 40 and 60 cm in length is compared with that of no 1 tubing 40 cm in length No 2 tubing was made of medium firm black rubber, with an outside diameter of 13 mm and an inside diameter of 7.5 mm It will be seen that the response curve for tubes 40 cm long indicates that transmission through them is not quite as good as when the column of air is smaller The curves for other lengths are similar, except for peaks due to resonance at different frequencies

Tubings no 3 and no 4 were made of soft gum rubber, the former had an outside diameter of 10 mm and an inside diameter of 6.5 mm, and the latter had an outside diameter of 8 mm and an inside diameter of 4.5 mm. Figure 4 C shows again that with larger columns of air transmission is somewhat poorer than with the standard unit. Except for fluctuations due to resonance similar results were obtained with tubing 20 and 60 cm in length. No 4 tubing had an inside diameter

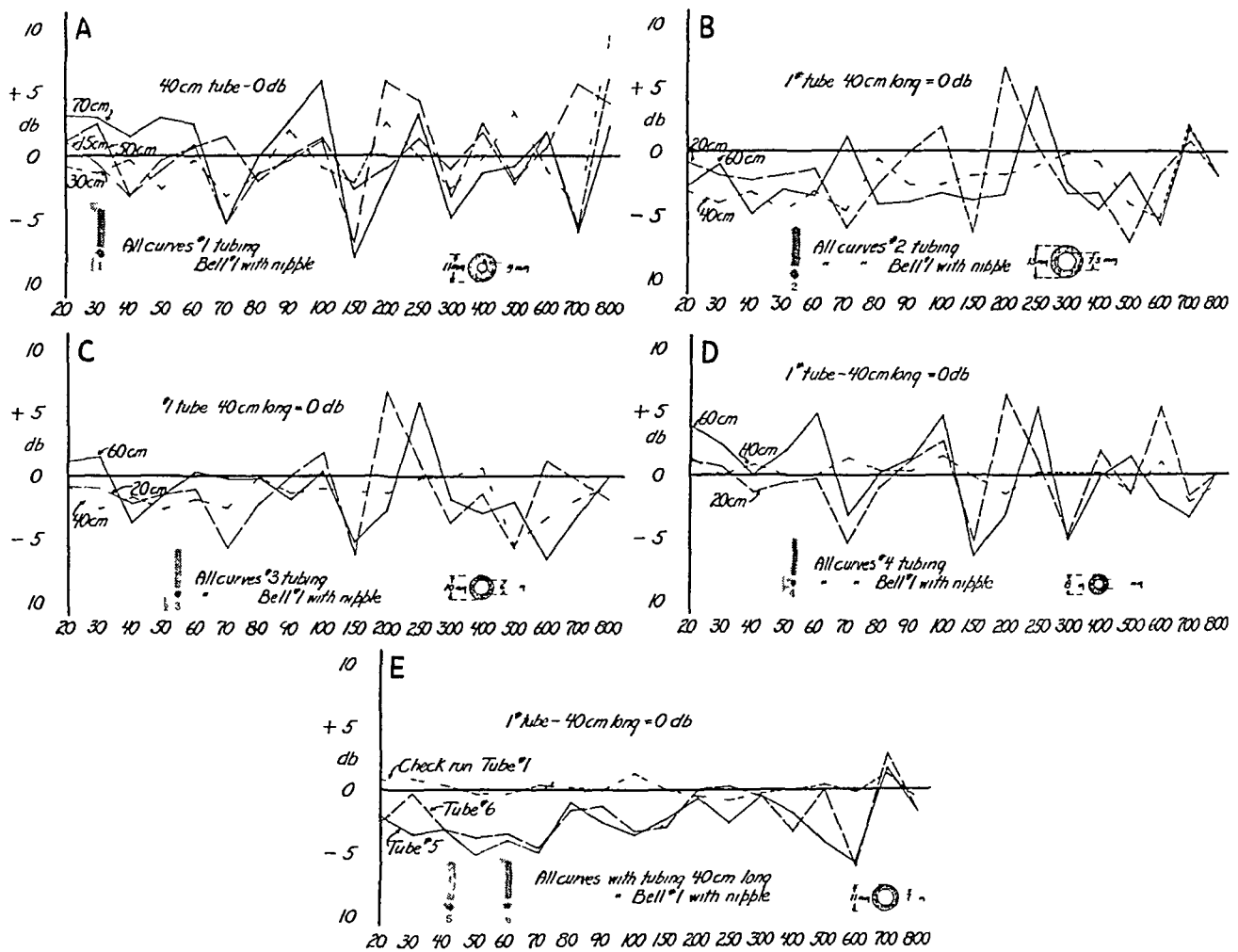


Fig 4—The results of tests on different lengths and types of tubing

only slightly greater than that of no 1 tubing, and in figure 4 D the curve for the 40 cm length is seen to follow the 0 axis closely. It is apparent that the physical characteristics of the rubber are a negligible factor in determining the response of a stethoscope. This point is further emphasized in the response curves for 40 cm lengths of no 5 and no 6 tubing seen in figure 4 E. Both of the tubes had an outside diameter of 11 mm and an inside diameter of 7 mm and were made of stiff red rubber. No 5 tubing was cut from new stock, while no 6 tubing had been in the laboratory for a long time and was harder

and more rigid than the no 5 tubing. The size of the air column in these tubings was intermediate between that of no 2 and no 3 tubing, and the response curves are seen to agree with those for the 40 cm tubes in figure 4 *B* and *C*. The curve made up of short dashes in figure 4 *E* was obtained, after all the different kinds of tubing had been tested, by repeating the frequency run on 40 cm lengths of no 1 tubing. The small deviation from the 0 decibel line indicates that the bell on the wall of the chest remained in constant position throughout all the tests of this group.

COMMENT

A few important general statements regarding stethoscopes can be made from the results just presented. The response of any unit will depend both on the type of end piece and on the character and arrangements of the tubes employed, but the present studies indicate that satisfactory transmission is much more dependent on the choice of the end piece than on the nature of the tubes. A similar conclusion is supported by theoretic considerations, for whenever transmission of sound from a dense to a rare medium takes place a serious loss of vibratory energy occurs, which is due to reflection of sound waves back into the dense medium. It can be shown that a properly designed end piece may increase manyfold the power transmission across the boundary between a solid or a liquid medium in which vibrations have originated and the air. Stewart and Lindsay² discussed the principle of the stethoscope in detail and showed that the transmission of sound energy from water to air can be greatly increased by the use of a simple end piece, consisting of a large shallow chamber connected with a listening tube of much smaller diameter.

It is evident that an end piece with a large aperture exposed to the vibrating chest should display better characteristics for transmission of sound than a similar unit with a small opening. The favorable response of bell no 9 (fig 2 *G*) and the poor showing of the small bell of unit 13 (fig 3 *B*) are probably due largely to the difference in the effective area for receiving sound waves. Bells having nearly the same effective aperture may differ considerably in their response, however. Thus, the bell of type 1, with a shallow chamber, is superior to bells of types 5, 6 and 10, which differ from the standard unit not only because they lack the shallow air chamber but also because the column of air enclosed in the bell is large. In this connection it is of interest to note that several years ago Barss, Eade and Fitzgerald,³ in one

² Stewart, G. W., and Lindsay, R. B. *Acoustics*, New York, D. Van Nostrand Company, Inc., 1930.

³ Barss, W. R., Eade, W. F., and Fitzgerald, E. B. *Boston M. & S. J.* **195** 116 (July 15) 1926.

of the few scientific studies of transmission of sound through stethoscopes to be found in the American literature, concluded that of a number of end pieces of the bell type with apertures of the same size, the units with small air chambers were best. Their work was done before many of the instruments now considered as essential in an acoustics laboratory were available, but although the units tested were suspended in air and were not in contact with a solid vibrating medium, the results are of interest.

These considerations lead us to believe that the most satisfactory type of bell is one with as large an aperture as is practicable, say 3 cm in diameter, and a shallow air chamber. From a theoretic standpoint the chamber should be as shallow as possible, but for use on the wall of the chest a depth of not less than 3 to 5 mm is probably necessary. The column of air leading from the terminal chamber should not be more than 3 mm in diameter, and the small column should pass as far as possible up into the metal framework of the end piece and terminate, without abrupt change in cross section, in two columns of similar size with which the air channels of the rubber tubes are continuous. We have shown that tubes with small air passages conduct sounds of all frequencies tested somewhat better than tubes of larger cross section. For the ideal end piece tubes with small diameters should therefore be used.

It is fitting here to call attention to some of the acoustic studies on stethoscopes that have been carried out in Europe. Of these, the investigations of Landes,⁴ Martini⁵ and Tobler⁶ are of particular interest. These authors, however, were chiefly concerned with monaural units, and few data relating to binaural stethoscopes, particularly to the performance of different kinds of end pieces, are to be found. Landes stated the belief that rubber tubing was unsuitable for use with stethoscopes because of the large amount of sound energy absorbed by the rubber itself. He suggested that tubes made of metal would be more desirable in this respect. Recently Macfarlan⁷ published a short article on the acoustics of the stethoscope. He did not describe the units that he tested or tell how the results were obtained. His conclusion that "the unaided ear operates at greater efficiency than the ear aided by any type of stethoscope" is not so surprising if it is remembered that the ear really functions as a stethoscope when it is applied directly to the chest.

4 Landes, G. *Deutsches Arch f klin Med* **171** 607 (Oct) 1931

5 Martini, P. *Ztschr f Biol* **71** 3, 1920

6 Tobler, P. D. *Schweiz med Wchnschr* **60** 933 (Oct 4) 1930

7 Macfarlan, D. *Acoustics of the Stethoscope*, *J A M A* **110** 2068 (June 18) 1938

A final word must be said concerning the relation of this study to clinical medicine. We believe that the data we have presented indicate that some stethoscopes are better acoustic instruments in that they transmit more sound energy to the ear. We do not advise all physicians to discard the stethoscope to which they are accustomed for one that may be acoustically superior because, except for sounds that are so faint as to be nearly inaudible, the loudness of sounds through the instrument is of no importance. In general, however, it is important to have an intimate acquaintance with the kind of sound that one is listening for and to be able to differentiate and interpret properly what is heard. In diagnosis of cardiac disease training and experience are more essential than a perfect stethoscope.

SUMMARY AND CONCLUSIONS

A method is described for testing stethoscopes in an acoustic system similar to the one that is present during auscultation in the clinic.

The results with this method indicate that

1. The bell with a shallow chamber is superior to other end pieces of the bell type.

2. A rubber nipple placed over the terminal portion of a bell improves its performance.

3. The diaphragm of a Bowles end piece acts as a filter to suppress the transmission of low-pitched sounds, but the diaphragm must be stiff to be effective in this respect.

4. Although rubber tubings of different lengths, diameters and degrees of stiffness modify transmission, largely because of resonance phenomena, the differences are relatively small, and the response of a stethoscope depends more on the choice of the end piece than on the nature of the tubes that are used.

Dr. R. E. McCotter and members of his staff aided in obtaining the anatomic material used in this study, and Prof. L. N. Holland loaned the condenser microphone. Dr. Frank N. Wilson helped in the preparation of the paper.

ATYPICAL FACIAL NEURALGIA

DIAGNOSIS, CAUSE AND TREATMENT

MARK ALBERT GLASER, M D

LOS ANGELES

From 1908 to 1916 Sluder¹ wrote a series of articles in which he described a neuralgic pain based on involvement of the sphenopalatine ganglion and the sphenoid sinus. It was true that some patients with this peculiar pain were relieved by therapy directed toward the sphenopalatine ganglion and sphenoid sinus, but there was a group of other patients who were thought to have sphenopalatine neuralgia but whose pain Sluder himself was unable to relieve by this therapy. Pains of this variety were described by Oppenheim,² Cushing,³ Harris⁴ and Davis⁵. In 1924, for the first time, Frazier and Russell⁶ segregated a group of patients from those with characteristic trigeminal neuralgia and suggested that because of the peculiar nature of their pains, and for want of a better term, their disease be called "atypical neuralgia". In 1928 I⁷ segregated 143 patients with atypical neuralgia from those with typical trigeminal neuralgia and described the complete syndrome for the first time. In 1938 Beerman and I⁸ again described this syndrome, reporting 200 cases in detail.

From a clinical standpoint this atypical neuralgia has many things in common with true migraine, but, in addition, it has some points in

1 Sluder, G. Headaches and Eye Disorders of Nasal Origin, St. Louis, C. V. Mosby Company, 1918

2 Oppenheim, H. Textbook of Nervous Diseases, Edinburgh, O. Schulze & Co., 1911

3 Cushing, H. The Varieties of Facial Neuralgias, Am J M Sc **160** 157 (Aug.) 1920

4 Harris, W. Pain in Lesions of Central and Peripheral Nervous System, Brain **44** 557, 1921

5 Davis, L. E. Lesions of the Paratrigeminal Area, J A M A **80** 380 (Feb 10) 1923

6 Frazier, C. H., and Russell, E. C. Neuralgia of the Face. An Analysis of Seven Hundred and Fifty-Four Cases, with Relation to Pain and Other Sensory Phenomena Before and After Operation, Arch Neurol & Psychiat **11** 557 (May) 1924

7 Glaser, M. A. Atypical Neuralgia, So-Called. A Critical Analysis of One Hundred and Forty-Three Cases, Arch Neurol & Psychiat **20** 537 (Sept) 1928

8 Glaser, M. A., and Beerman, H. M. Atypical Facial Neuralgia. An Analysis of Two Hundred Cases, Arch Int Med **61** 172 (Feb) 1938

common with neuralgias of the cranial nerves, particularly with trigeminal neuralgia. In some instances it so closely simulates trigeminal neuralgia that an injection of alcohol is necessary to differentiate one from the other. In the earlier work of Frazier and Russell and of Cushing a number of patients with what seemed to be trigeminal neuralgia were subjected to major operation on the trigeminal tract, and it was only because of the continuation of pain in spite of anesthesia that it was realized that these patients had some other type of neuralgia. In fact, one may definitely state that there exists a type of neuralgia transitional between migraine and trigeminal neuralgia. Because this transitional neuralgia, which I have classified as "atypical neuralgia," may closely simulate both types, and, further, because many of the group with atypical neuralgia have an associated neurosis, considerable confusion in the nomenclature has existed, with the result that the same clinical syndrome has been given different names by various authors. These names have included psychalgia, facial neuralgia, sympathetic algia, pseudotrigeminal neuralgia, ciliary neuralgia, migrainous neuralgia, atypical migraine, allergic migraine, sympathetic neuralgia, neuralgic headache, senile neuralgia, cephalalgia, facial causalgia, cephalalgia of the jaw, sympathetic hemicrania, autonomic faciocephalic neuralgia, sphenopalatine neuralgia, vidian neuralgia and psychogenic neuralgia.

In the past ten years some progress has been made in determining the sensory supply of the face, as well as in classifying the various clinical entities which could produce the pain of atypical neuralgia.⁹

9 (a) Reid, M. R., and Eckstem, G. Sensory Disturbances Following Sympathectomy for Angina Pectoris, *J. A. M. A.* **83** 114 (July 12) 1924. (b) Fay, T. Atypical Neuralgia, *Arch. Neurol. & Psychiat.* **18** 309 (Aug.) 1927. Atypical Facial Neuralgia, a Syndrome of Vascular Pain, *Ann. Otol., Rhin. & Laryng.* **41** 1030 (Dec.) 1932. (c) Parker, H. L. Unusual Forms of Pain in the Area of the Fifth Nerve, *J. A. M. A.* **83** 1672 (Nov. 22) 1924. (d) Foerster, O. *Deutsche Ztschr. f. Nervenh.* **106** 109 (Dec.) 1928. (e) Halphen, Monbrun and Tournay. Les cephalées en oto-neuro-ophtalmologie (physiologie pathologique et traitement), *Rev. d'oto-neuro-opht.* **7** 161 (March) 1929. (f) Peet, M. M. The Role of the Sympathetic Nervous System in Painful Diseases of the Face, *Arch. Neurol. & Psychiat.* **22** 313 (Aug.) 1929. (g) Grant, F. Personal communication to the author, Jan. 20, 1930. (h) Flothow, P. G. Relief of Pain from a Neurological Viewpoint, *Northwest Med.* **29** 69 (Feb.) 1930. (i) White, J. C. Progress in the Surgery of the Sympathetic Nervous System in 1932, *New England J. Med.* **209** 843 (Oct. 26) 1933. (j) Mixer, J. J., and White, J. C. Pain Pathways in the Sympathetic Nervous System, *Arch. Neurol. & Psychiat.* **25** 986 (May) 1931. (k) Reichert, F. L. Neuralgias of Head and Face, *Am. J. M. Sc.* **187** 362 (March) 1934. (l) Davis, L. *Neurological Surgery*, Philadelphia: Lea & Febiger, 1936. (m) Abbott, W. D. Diagnostic and Therapeutic Injection of the Sympathetic Nervous System, *Nebraska M. J.* **17** 293 (July) 1932. (n) Wilson,

Though both these problems still remain perplexing, and though considerable confusion exists, an attempt will be made in this contribution to classify the various pain syndromes producing atypical neuralgia, as well as to consider the various phases of present methods of therapy. This pain need no longer be looked on as incurable. However one must still be ultraconservative in carrying out therapeutic measures, as

D C Atypical Facial Neuralgia, *J A M A* **99** 381 (Sept 3) 1932 (o) Fincher, E, in discussion on Wilson⁹ⁿ (p) Turner, C C, in discussion on Wilson⁹ⁿ (q) Braeucker, W Die Fortschritte und die Zukunft der Sympathicuschirurgie, *Nervenarzt* **6** 449, 1933, Ueber typische und atypische Formen von Gesichtsnuralgien, *Zentralbl f Chir* **60** 2454, 1933 (r) Marks, S B Sympathetic Nervous System as a Causative Factor in Atypical Neuralgia, *Kentucky M J* **32** 393 (Aug) 1934 (s) Bryan, A W Neuralgias of the Head and Neck, *Wisconsin M J* **34** 320 (May) 1935 (t) Hyslop, G H Face Pain, *New York State J Med* **36** 91 (Jan 15) 1936 (u) Brickner, R M, and Riley, H A Autonomic Facio-Cephalalgia, *Bull Neurol Inst New York* **4** 422 (Dec) 1935 (v) Merwarth, H R, and Freimann, I Practical Neurologic Therapy, *M Times & Long Island M J* **64** 2 (Jan) 1936 (w) Cobb, S, and Mixer, J Lingual Spasm, *Ann Surg* **101** 49 (Jan) 1935 (x) Weisenburg, T H Cerebellopontile Tumor Diagnosed for Six Years as Tic Douloureux The Symptoms of Irritation of the Ninth and Twelfth Cranial Nerves, *J A M A* **54** 1600 (May 14) 1910 (y) Harris, W Neuritis and Neuralgia, London, Oxford University Press, 1926 (z) Doyle, J B A Study of Four Cases of Glossopharyngeal Neuralgia, *Arch Neurol & Psychiat* **9** 34 (Jan) 1923 (a') Sicard, R, and Robineau Algie velo-pharyngee essentielle Traitement, chirurgical, *Rev neurol* **27** 256, 1920 (b') Reichert, F L Glossopharyngeal Neuralgia, *West J Surg* **39** 347 (May) 1931 (c') Adson, A W The Surgical Treatment of Glossopharyngeal Neuralgia, *Arch Neurol & Psychiat* **12** 497 (Nov) 1924 (d') Dandy, W E Glossopharyngeal Neuralgia (Tic Douloureux) Its Diagnosis and Treatment, *Arch Surg* **15** 198 (Aug) 1927 (e') Stookey, B Glossopharyngeal Neuralgia Surgical Treatment, with Remarks on the Distribution of the Glossopharyngeal Nerve, *Arch Neurol & Psychiat* **20** 702 (Oct) 1928 (f') Fay, T Intracranial Division of Glossopharyngeal Nerve Combined with Cervical Rhizotomy for Pain in Inoperable Carcinoma of the Throat, *Ann Surg* **84** 456, 1926 (g') Avellis, G Typische Form von Kehlkopfneuralgie, *Munchen med Wchnschr* **47** 1592 (Nov 13) 1900 (h') Hutter, F Ueber Neuralgien des Nervus laryngeus superior, *Monatschr f Ohrenh* **63** 402 (April) 1929 (i') Bailey, P Neuralgias of Cranial Nerves, *S Clin North America* **11** 61 (Feb) 1931 (j') Echols, D H, and Maxwell, J H Superior Laryngeal Neuralgia Relieved by Operation, *J A M A* **103** 2027 (Dec 29) 1934 (k') Hunt, J R Otalgia Considered as an Affection of the Sensory System of the Seventh Cranial Nerve, *Arch Otol* **36** 543, 1907 (l') Clark, L P, and Taylor, A S True Tic Douloureux of the Sensory Filaments of the Facial Nerve Cure Effected by Physiologic Excirpation of Genuiculate Ganglion, *J A M A* **53** 2144 (Dec 25) 1909 (m') Reichert, F L Tympanic Plexus Neuralgia True Tic Douloureux of the Ear or So-Called Genuiculate Ganglion Neuralgia, Cure Effected by Intracranial Section of the Glossopharyngeal Nerve, *ibid* **100** 1744 (June 3) 1933 (n') Hall, G W Auricular Neuralgia, *Arch Neurol & Psychiat* **29** 615 (March) 1933

has previously been emphasized. The physician should refrain from any surgical measures unless he is absolutely certain of the diagnosis. It must still be remembered that incorrectly chosen procedures, such as operations on the trigeminal tract, surgical removal of the sphenopalatine ganglion, extraction of teeth, operations on the nose and the nasal sinuses, sympathectomies, mastoidectomy and abdominal operations, carried out indiscriminately in poorly chosen cases will do far more harm than good and leave the patient in a much worse condition than before the operation. I cannot too urgently advise caution in arriving at a decision for operative measures.

These atypical facial neuralgias may be classified under four main types. Type 1 is the primary atypical neuralgia, for which at present no cause can be ascertained and for which the treatment must be directed toward the blockage of sensory pathways. The diagnosis is reached only by a process of elimination. Without doubt, in the future this type can be removed from many neuralgias of definite, known cause. In neuralgia of type 2, a series of clinical entities gives rise to pain of an atypical nature. Treatment naturally must be directed toward the disturbances. However, the blockage of nerves is necessary for the relief of pain. In neuralgia of type 3, generalized systemic diseases are responsible for the pain. In type 4 an associated pathologic condition of the head, the neck or the abdomen exists, and the neuralgia disappears in most cases with elimination of the abnormality. In all of these types, if the neuralgia does not disappear, specific medical or surgical treatment directed toward the sympathetic system should be employed. It is well to mention here that though this classification and the therapeutic suggestions might indicate that the entire problem of atypical neuralgia has been solved, the physician will still be confronted with a group of unfortunate patients whom he cannot relieve of pain. Thus the problem remains one for further research, with the hope that eventually all these patients can be assured of complete relief from this annoying, painful condition.

CLASSIFICATION OF ATYPICAL FACIAL NEURALGIA

- I Primary atypical facial neuralgia
- II Secondary atypical neuralgia due to various clinical entities
 - 1 Sphenopalatine and vidian neuralgia
 - 2 Postherpetic trigeminal neuralgia
 - 3 "Trigeminal ghosts"
 - 4 "Trigeminal ghosts" with lingual spasm
 - 5 Syndrome due to abnormalities of the mandibular joint
 - 6 Autonomic faciocephalgia
 - 7 Painful convulsive tic
 - 8 Headache due to hypertonicity of muscles of the neck
 - 9 Senile neuralgia

III Atypical facial neuralgia produced by systemic diseases

- 1 Allergy
- 2 Endocrine disturbance
- 3 Psychoneurosis

IV Atypical facial neuralgia due to lesions of the head, chest and abdomen

- 1 Infections about the head
 - (a) Mastoiditis
 - (b) Thrombosis of the cavernous and longitudinal sinuses
 - (c) Deep-seated facial abscess
- 2 Tumors of the head and neck
- 3 Intracranial lesions
- 4 Dental sepsis
- 5 Deviations and spurs of the nasal septum
- 6 Ocular lesions
- 7 Lesions of the chest
- 8 Pathologic conditions in the abdomen and pelvis

PRIMARY ATYPICAL FACIAL NEURALGIA

The clinical picture of primary atypical neuralgia has previously been discussed in detail. It differs distinctly from that of acute neuralgias secondary to involvement of the trigeminal, facial, glossopharyngeal, vagus and cervical nerves. The primary type of atypical neuralgia has had one distinct point of differentiation from the secondary types. All the cases of primary atypical neuralgia which have come under my observation and in which there was great difficulty in the relief of pain were cases in which the pain had been present for a year or more. This pain is never superficial, is always deep seated and is aching, burning or throbbing. The patients find great difficulty in describing the sensation accurately. From their accounts of the pain, I have assembled a list of some seventy descriptive terms, such as dull, aching, throbbing, burning, shooting, sharp, drawing, needle-like, boring, pulling, gnawing, bursting, tearing, tingling, smarting, nagging, knifelike, beating, stinging, pricking, itching, gripping, lightning-like, twitching, severe, jumpy, crawling, unbearable, wearing, pounding, surging, crushing, vibrating, excruciating and grabbing. The pain has been described as a sense of pressure, as toothache or soreness and as an electric shock, a hot iron, bugs creeping, tearing celery, a thousand fishhooks pulling and tugging on the face, birds flying under the skin, the pounding of a hammer on the face, a hot poker back of the eye, the cutting away of pieces of bone or muscle beneath the skin, a bruise, a saw cutting the face, something in the jaw, a mass of fire, pins and needles, stiffness, the feeling of menthol, the buzzing of a mosquito, tongs on top of the head, a full feeling, a hard knot deep in the eye, the bursting of an eyeball, the pushing of the eye through the head, drawing out the eye or a ball of fire or electricity in the eye.

In about one half of this series of 245 cases the onset of pain could not be attributed to any cause, though numerous coincidental events were thought by the patients to be responsible for their difficulties. Thirty-eight patients felt that pain followed the extraction of teeth, 16 remembered that the onset of pain was shortly after an accident, whereas 13 believed the pain followed surgical treatment and 6 named numerous minor conditions as the cause of the complaint. It is apparent from this study that no particular factor could be held responsible for the onset of this pain and that the events named were coincidental, except possibly the extraction of teeth. Tic douloureux affected the two sexes equally, whereas atypical neuralgia affected chiefly females. Bilateral pain occurred in only 2 per cent of the cases of tic douloureux, while it was found in 33 per cent of the cases of atypical neuralgia.

The distribution of the pain in trigeminal neuralgia was always in the areas supplied by the trigeminal nerve, whereas in atypical neuralgia a circular area within the distribution of the vascular supply of the face and head was affected. The pain was felt in the chin, along the nose, around the eye, over the brow, to the vertex or to the temporal region, in front of, in or through the ear and thence down into the suboccipital region. Occasionally it entered the shoulder, rarely the body. This wide area of distribution might occur in a single case or there might be individual areas or various combinations of areas (fig. 1).

The pain of trigeminal neuralgia is brought on by the slightest local contact, and trigger zones occur over the facial foramina. In the cases of atypical neuralgia there was occasional tenderness over the cervical sympathetic ganglion or over the carotid artery. The pain of atypical neuralgia was aggravated by such local factors as cold, draft, heat, eating, light, contact, brushing the teeth, vibration, reading, wind, blowing the nose, sneezing, swallowing and shaving, and by such general factors as fatigue, excitement, menstruation, worry, talking, winter conditions, exertion, lying down, stooping, noise, dampness, motion, cough, argument, washing the face and constipation. It might be worse in the morning or at night.

Sympathetic phenomena were present in about 50 per cent of the cases of atypical neuralgia and were never present in trigeminal neuralgia. These sympathetic phenomena consisted of ocular disturbance, such as lacrimation, edema, corneal injection, inequality of the pupils, blurred vision, photophobia and enophthalmos. In addition, the following symptoms, some of which are common in migraine, were sometimes present: nausea, vomiting, flushing of the face, nasal discharge, perspiration, salivation, puffiness of face, feeling of warmth, ringing in the ears, soreness over the temporal artery, chills and aural discharge.

Outstandingly different from trigeminal neuralgia is the continuous nature of this deep-seated, aggravating pain without periods of relief. As has been previously mentioned, trigeminal neuralgia manifests itself by momentary attacks of excessively severe pain. The patient with atypical neuralgia has a continuous pain of more annoying, aggravating nature, disturbing by its persistence and chronicity rather than by its severity. Superimposed on this chronic pain in the majority of cases were attacks of greater or lesser severity, which came on either acutely or insidiously. If an attack of pain had an insidious onset, it gradually increased in intensity over a period of from several hours to several days. Then the

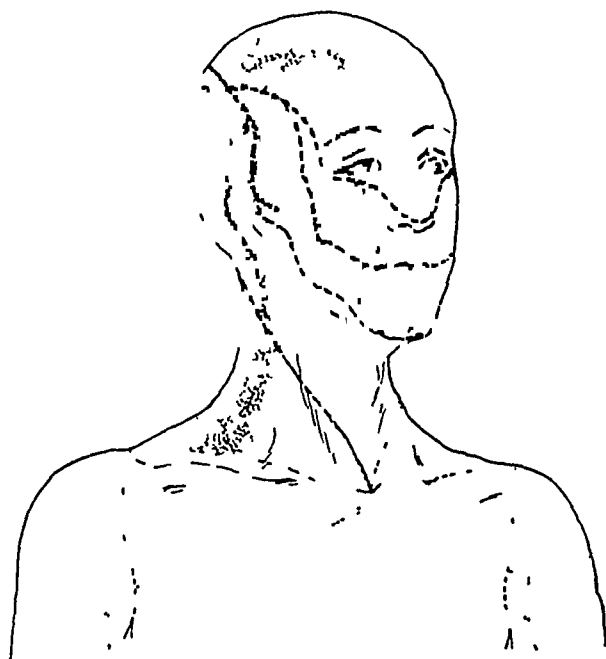


Fig. 1—Maximum distribution of pain in atypical neuralgia. The dashes represent the sensory distribution of the trigeminal nerve, the dots represent the distribution of pain in atypical neuralgia. Note how the pain zone of atypical neuralgia crosses beyond the bounds of the trigeminal sensory supply.

pain would be at its height for several hours to several days. During this period of most severe pain associated sympathetic phenomena were present in some cases, and the patient was necessarily confined to bed. The pain might then either suddenly subside or gradually disappear. These attacks might occur at intervals of several days or even of months, but during the interim the patient was never free from pain. This phase of the disease picture demonstrates the close relation of atypical neuralgia to migraine, and an even closer relation to migraine is shown by the fact that a small number of patients has such attacks frequently with only a minor persistent ache, or even at times with no ache, in the intervals. Another small group of these patients has a type of neuralgia more

closely allied to the trigeminal form in that their attacks may last for a half-hour to several hours and occur rather frequently in the day during a period of susceptibility. On close questioning it is found that the character of the pain differs from that of true trigeminal neuralgia. At times, however, one cannot differentiate the picture of atypical neuralgia from that of clinical trigeminal neuralgia, and an injection of alcohol is used as a therapeutic test. Addiction to narcotics is common among patients with atypical neuralgia, but not among those with trigeminal neuralgia.

Most of the patients with primary atypical neuralgia have an associated neurosis, a fact which has led many to believe that the entire group is psychoneurotic. However, one may readily see how a psychoneurosis might develop secondary to this persistent, annoying, irritating pain from which no relief can be secured. It seems closer to the truth to take this view than to consider the whole picture that of a nervous patient. It is true of course that some of these patients are definitely psychoneurotic, but their condition will be considered in detail under the secondary types of atypical neuralgia.

SECONDARY ATYPICAL FACIAL NEURALGIA

In this series of 245 patients with atypical neuralgia, 143 belong to the group reported on in Philadelphia.⁷ None of these 143 patients could be relieved of the pain. Of the first 50 patients of the second group observed, only about 10 per cent were relieved. Of the next 25 patients, approximately 65 per cent were found to have secondary conditions and about 50 per cent were relieved of symptoms. In 85 per cent of the last 27 patients the cause of the pain was determined, and in 75 per cent the symptoms were relieved. It is of interest that most of the patients with secondary atypical neuralgia had had their pain for only a short time, from several days to three months, in contradistinction to those with the primary type, who had had the pain for a year or more before they came under my observation. From a clinical standpoint, the best curative results were obtained with those patients whose pain was of short duration.

Sphenopalatine Neuralgia—As a result of anatomic studies, Sluder pointed out in 1909 the close relationship between the sphenopalatine ganglion in the sphenomaxillary fossa and the nose or the accessory sinuses. The ganglion was sometimes situated within 1 or 2 mm of the nasal mucosa, and at times it was as deep as 7 to 9 mm. The bony wall separating the fossa from the ganglion is very thin. It is a well known fact that inflammatory processes of the sphenoidal, the post-ethmoid and the maxillary sinus may extend to the optic nerve. There-

fore, Sluder assumed that such inflammations could extend to Meckel's ganglion, producing pain rather than the blindness secondary to involvement of the optic nerve

After an observation of 47 cases, Sluder gave the following description of the syndrome

Pain, which begins at the root of the nose, extends downward over the maxilla and backward in the mastoid to become severest about 5 cm posteriorly to its tip, thence extending backward to take in the entire occiput, and downward into the neck, shoulder blade, shoulder, and sometimes into the axilla. With the severest attacks it extends down into the arm, forearm, hand and even to the fingers. According to my observations, this pain very rarely invades the upper part of the head. When very severe it may extend a little way into the brow, or somewhat above the line of the zygoma. I have seen this picture complicated by or associated with other headaches, but the distinctive "neuralgic phenomena," as outlined above and which have proved uniformly amenable to treatment (cocainization of the nose) have not extended to the upper part of the head¹⁰

From this distribution which he described, Sluder derived his term "lower headaches"

In addition to the symptom of pain, Sluder described sensory signs which consisted of slight anesthesia of the soft palate, the pharynx, as far down as the lower part of the tonsil, and the lower anterior part of the nose. He also found such motor signs as a deflected uvula and a high palatine arch on the affected side.

In the movement of the soft palate in closing off the nose from the throat, the median raphe was deflected from the affected side, and the dimple which formed just above the uvula during this act was displaced to the well side. Normally it is in the median line.

Gustatory changes were almost always diminished or delayed on the affected side.

A sympathetic syndrome consisting of vasomotor and secretory disturbances might exist with or without the headache. These disturbances consisted of a slight coryza, which developed suddenly with an explosive effect and was associated with protracted sneezing and with nasal congestion, accompanied by thin, hot secretions so profuse as to cause the patient to resort to a towel. The eyes became reddened and bathed in tears, and sometimes itched or burned, and the pupils were sometimes dilated.

Vidian Neuralgia—Inflammation of the sphenoid sinus may present a picture identical with that of neuralgia which starts in the sphenopalatine ganglion, and suggests the anatomic explanation that the nerve trunks going to the ganglion (the vidian and the branch from the second division of the fifth nerve) may, by reason of their proximity

¹⁰ Sluder, G. Relation of Sphenopalatine Ganglion to Nose, Tr. Am. Laryng. A., 1909, p. 329.

to the sphenoid sinus, become readily inflamed in sphenoiditis. The differential diagnosis can be made from the fact that cocaineization of the ganglion controls the pain when it originates in the ganglion but fails to stop it when it originates in the sphenoid sinus because the ganglion is peripheral to the point of origin. Cocaine applied within the sphenoid sinus, however, does not always stop the pain originating there.

Sluder stated that by electrical stimulation of the vidian nerve in the sphenomaxillary fossa he was able to produce experimentally pain in the ear, mastoid, occiput, neck, shoulder blade, shoulder, arm, forearm and hand, and he used the term "vidian neuralgia" to describe such a distribution of pain. He also stated that the pain in the teeth, the eye and the temple in neuralgia of Meckel's ganglion is referable to the anterior, or maxillary, component. He reported several cases of vidian neuralgia and described tic of the vidian nerve as "sharp, recurrent, stabbing attacks of pain in the lower half of the head, in the neck and shoulder, at intervals of not more than a few hours apart."

Schaeffer,¹¹ Sluder,¹ Onodi,¹² Grunwald,¹³ and many others described the intimate relations between the sphenoid sinus and the vidian nerve running in the vidian canal. This intimate relation is due chiefly to pneumatization of the pterygoid process and even of the pterygoid plates. Many anatomic preparations show the vidian canal running as a prominent ridge through the floor of the sphenoid sinus with recesses or prolongations of the sinus median and lateral to the canal. Delusances in the bony wall of the canal may place the mucosa of the sinus in direct contact with the nerve sheath. The large type of sphenoid sinus with recesses and prolongations is more subject to what Canuyt, Ramadier and Velter¹⁴ have termed latent sinusitis. These authors stated that sphenoid sinusitis is a serious condition without much tendency to spontaneous healing, particularly when there are prolongations extending deep into the pterygoid plates or into the wings of the sphenoid bone.

The two chief factors in the production of vidian neuralgia are (1) infection of the mucosa of a large sphenoid sinus and (2) a thin bony

11 Schaeffer, J. P. *The Nose, Paranasal Sinuses, Nasolacrimal Passageways and Olfactory Organ in Man*, Philadelphia, P. Blakiston's Son & Co., 1920.

12 Onodi, L. *Die Beziehungen des Canalis Vidianus, des Nervus petrosus superficialis major und des Nervus petrosus profundus zur Keilbeinhöhle*, *Monatschr. f. Ohrenh.* **53** 377, 1919.

13 Grunwald, L. *Descriptive und topographische Anatomie der Nasen und ihrer Nebenhöhlen*, in Denker, A., and Kahler, O. *Handbuch der Hals-Nasen-Ohrenheilkunde*, Berlin, Julius Springer, 1925, vol. 1, pp. 1-95.

14 Canuyt, G., Ramadier, J., and Velter. *Les sinusites postérieures et leurs complications oculaires*, *Ann. d. mal. de l'oreille du larynx* **44** 39 (Jan.), 140 (Feb.) 1925.

wall of the vidian canal, with or without dehiscences. Vail¹⁵ expressed the opinion, based on further anatomic study, that sphenopalatine and vidian neuralgias are really the same syndrome, that the vidian nerve rather than the sphenopalatine ganglion should be considered as the etiologic basis and that the neuralgia is really due to irritation or inflammation of the vidian nerve in the vidian canal and is always secondary to latent or frank infection in the sphenoid sinus. He said that proper treatment should be directed toward the disease in the sphenoid sinus.

This syndrome in every way represents the clinical picture of certain neuralgias. The fact that this entire pain picture is not always produced by the inflammations described by Sluder and Vail and that procedures directed toward the sphenopalatine ganglion or toward the sphenoid sinus do not relieve patients with this syndrome is sufficient reason for the assumption that other and varied causes may produce a similar clinical picture. This is further justified by the fact that a number of the patients in this series with so-called atypical neuralgia were referred to Sluder himself and ran the gamut of operative procedures directed toward the sphenopalatine ganglion and the sphenoid sinuses without relief of pain. It is true that a great number of patients with atypical neuralgia can be relieved of pain by such operations, and in my own experience this is particularly true of the patients treated in the acute stages. To attribute all pain of this type to either sphenopalatine or vidian neuralgia, however, would confine therapeutics to too narrow a field and result in innumerable failures, as I have indicated in my previous reviews on this subject. For this reason it is preferable to look on this unusual syndrome as a type of atypical neuralgia, and should operative therapy directed toward the sphenopalatine ganglion and sphenoid sinuses fail, attention should be directed to the other methods available. It is advisable to be ultraconservative in the use of more radical surgical measures, particularly those directed to the sinuses, because of the great number of failures that result from such procedures. Only in those cases in which clearcut sinusitis exists should operation be considered. In my own series, 8 such patients were relieved by repeated cocaineization of the sphenopalatine ganglion plus the use of mild sedatives and occasional supplementation with trichloroethylene.

Postherpetic Trigeminal Neuralgia—Herpes referred to the various divisions of the trigeminal nerve, particularly the ophthalmic portion, is

15 Vail, H. H. Vidian Neuralgia from the Disease of the Sphenoidal Sinus. Report of a Case, *Arch Surg* **18** 1247 (April) 1929, Vidian Neuralgia, *Ann Otol, Rhin & Laryng* **41** 837 (Sept.) 1932, Vidian Neuralgia, with Special Reference to Eye and Orbital Pain in Suppuration of the Petrous Apex, *Arch Otolaryng* **17** 212 (Feb.) 1933, Pathways of Reflex Pain in Vidian Neuralgia, *ibid* **21** 277 (March) 1935.

associated with severe, sharp pains of a continuous nature during the acute stage. Occasionally, however, the character of this pain changes as the herpetic lesions subside and resembles that of atypical neuralgia. This pain may continue for years, and ordinary methods for its relief may prove futile. In spite of the fact that the pain continues indefinitely and that the patients complain rather persistently of the continuous pain, they, like the patients having other kinds of atypical neuralgia, show no signs of pain on examination, as indicated by their facial expressions. The 4 patients who came under my observation had pain referable to the ophthalmic division, and all of them were extremely hesitant even to have nerve block performed when absolute assurance of cure could not be given. This fact makes one wonder whether the pain is actually as severe as these persons wish one to believe. In all cases the scars of the previous vesicles still remained. The fact that the patients complained of a continuous pain which in every way simulated atypical neuralgia proper is sufficient indication of its organic character in some cases. Thalhimer¹⁶ described perivascular infiltrations in the pons extending upward to the internal capsule in a case of cervical herpes zoster. Peet¹⁷ said that such a lesion might furnish the satisfactory explanation for the persistence of pain after section of the sensory root, especially if the lesion was located in the trigeminal portion of the thalamus. Thus, one would have an explanation of this pain on the basis of central pain, which again would complicate the picture of so-called atypical neuralgia. Relief was obtained by Harris¹⁷ after injection of alcohol in the gasserian ganglion. Peet obtained only questionable relief in 2 cases by section of the sensory root. Treatment of the autonomic system will, without doubt, eventually offer some means of relief.

"Trigeminal Ghosts"—To neurosurgeons who have performed any great number of operations on the trigeminal tract the occurrence of a characteristic atypical pain of an extremely severe and practically continuous nature is not new. Fortunately, this annoying, irritating pain is extremely rare. Cobb and Mixer,¹⁸ Frazier and Russell,¹⁹ Harris and I have described this pain. Cobb and Mixer reported 3 cases of lingual spasm following the advent of the atypical neuralgia. The spasm was always on the side of operation and usually came on with fatigue, as in prolonged speaking, or with local irritation to the tongue during eating. The lingual spasm was relieved by resection of the lingual nerve through the mouth. In this particular instance the spasm was associated with vasodilatation of one half of the tongue. Cobb and Mixer stated the

16 Thalhimer, W. Herpes Zoster. Central Nervous System Lesions Similar to Those of Epidemic (Lethargic) Encephalitis. Report of a Case, *Arch Neurol & Psychiat* 12:73 (July) 1924.

17 Harris, W. The Facial Neuralgias, London, Oxford Medical Publications, 1937.

belief that nerve impulses persisted through the autonomic branch from the geniculate ganglion of the facial nerve. The spasm may be relieved by cutting the chorda tympani fibers in the lingual nerve. Harris, McLean¹⁸ and Flothow and Smith¹⁹ reported some success in relieving this pain by procedures on the stellate ganglion. Three patients in my series had pain of this type. One ran the gamut of medical treatments and injections without recovery from pain. The other was relieved to a great degree by acetylcholine. The third patient had a subtotal root resection. Atypical pains with some trigeminal characteristics developed deep in the eye and over the first division of the fifth nerve. A peripheral neurectomy was performed on the first division, producing some relief in the lancinating character of the pain. The patient then gained relief from this deep-seated, burning pain by the instillation of cocaine into the eye for about four months, by the instillation of atropine into the eye for three months and by the inhalation of amyl nitrite for an additional three months. Because he complained bitterly of pain in his eye, particularly in bright lights, he was given dark glasses, which relieved him somewhat. It was then decided to try the effect of suturing his eyelids together. This has relieved the deep pain in the eyeball for a further period of two months.

Syndrome Due to Abnormalities of the Mandibular Joint—Maloccluding original teeth, lack of molar teeth on one side or badly fitting dental plates, permitting overclosure, result in anatomic changes which produce this syndrome. These anatomic changes cause erosion of the bone either of the glenoid or of the mandibular fossa, with impaction of the condyles against the thin bone separating them from the dura. These condyles then move backward or mesially in controllable movements and, according to Costen, irritate the auriculotemporal nerve. Incidentally, they also irritate the chorda tympani nerve. The syndrome consists of atypical headaches, mild catarrhal deafness, occasional dizzy spells, glossodynia and occasional herpes.

The treatment consists of reposition of the jaws by slowly increasing the vertical dimension of the jaw. The interposition of a disk between the molar teeth helps to verify the diagnosis, and the problem then becomes one of conservative or radical surgical measures. Two patients in my series were not relieved by this method, but they refused oral surgical treatment.

18 McLean, A. J. Intractable Facial Pain. Relief by Deep Injections of Alcohol, *Northwest Med* **32** 16 (Jan) 1933.

19 Flothow, P. G., and Swift, G. W. Surgery of Sympathetic Nervous System. Review of One Hundred Sympathetic Ganglionectomies, *Am J Surg* **21** 345 (Sept) 1933. Flothow, P. G. Injection of Sympathetic Nervous System, *California & West Med* **44** 182 (March) 1936, personal communication to the author, 1938.

Autonomic Faciocephalgia—From the group with atypical neuralgia of this kind Bückner and Riley²⁰ selected 3 patients who were amenable to treatment with ergotamine tartrate and with epinephrine. They pointed out the confusion of nomenclature between cases of atypical migraine and those of atypical neuralgia. Vallery-Radot and Blamoutier²⁰ reported a case in which a similar type of pain was relieved by the use of epinephrine. One cubic centimeter of epinephrine injected subcutaneously abolished all the pain within fifteen minutes, and it did not reappear until fourteen hours later. A gargle of 20 drops of a 1:1,000 solution of epinephrine in 2 teaspoonfuls of water gave mild relief of symptoms. Twenty subcutaneous injections of 1 cc of a 1:1,000 solution of epinephrine given over a period of seven weeks abolished the symptoms. These authors expressed the opinion that repeatedly induced constriction abolished the headache, which was dependent on vasodilatation and that such a headache was in contrast to that of migraine, which they believed was the result of vasoconstriction.

Basing their conclusion on these 4 cases, Bückner and Riley advanced the opinion that there are two types of headaches: one influenced by epinephrine (and presumably due to localized sympathetic hypofunction) and the other influenced by the supposed antagonist of epinephrine, ergotamine tartrate (and presumably dependent on localized sympathetic hyperfunction).

My own experience verifies this opinion of Bückner and Riley. Under my observation, 4 patients have been relieved by ergotamine tartrate, and 1 whose condition was classified as a "trigeminal ghost" was relieved temporarily by amyl nitrite. It is my opinion that patients having atypical neuralgia should be treated with the various vasoconstrictor and vasodilator drugs to determine whether their condition can be differentiated from the main group of atypical neuralgias.

Vallery-Radot and Blamoutier found that by immersing the hands of certain migrainous patients in ice water and by applying ice to the front of the head attacks of migraine could be induced. In my own experience, I have had under observation a number of patients whose attacks of migraine could be abolished for several hours by the application of ethyl chloride to the area of pain. As the area became frozen the pain wandered laterally to the parietal region and then disappeared.

Painful Convulsive Tic—The existence of the syndrome of atypical neuralgia with facial spasms could be differentiated from the usual

20 Vallery-Radot, P., and Blamoutier, P. Syndrome de vasodilatation hémicéphalique d'origine sympathique, *Bull et mém Soc méd d hôp de Paris* 49:1488 (Nov. 27) 1925.

variety This affliction is uncommon and few cases have been reported in the literature Cushing³ described 3 cases of his own and made note of an additional case supplied by a surgeon in Philadelphia The disease in these cases closely simulated trigeminal neuralgia The spasms were extremely severe and were associated with considerable pain In 3 cases operation on the gasserian ganglion and the facial nerve failed to relieve the pain In a fourth case the patient was relieved by spinofacial anastomosis Harris¹⁹ relieved a patient with this condition by injection of alcohol into the gasserian ganglion

In the present series 1 patient with this syndrome has been encountered This man had continuous pain of the atypical variety, associated



Fig 2—Facial expression during an attack of facial spasm associated with severe facial pain

with facial tic The pain was extreme, with exacerbations during the spasm He had several badly infected teeth, which were removed He was placed under treatment with mild sedatives and inhalation of ampules of trichloroethylene three times a day, and was told to practice the control of his facial tic before a mirror Within a week the spasms had greatly subsided, and the atypical neuralgia had improved about 85 per cent The patient was an active, stern, stable person, who continued his work in spite of his discomfort After relief of symptoms for about three months, he became worried because of marital difficulties Immediately his pain increased and his spasms were more frequent, but they were again relieved by increasing doses of sedatives (fig 2)

Headache Due to Hypertonicity of Muscles of the Neck —Peritz,²¹ Halle²² and Mithoefer²³ have called attention to a headache secondary to hypertonicity of muscles of the neck. They stated the belief that the hypertonicity is due to such abnormalities as dysfunction of the endocrine system and arthritis. Various authors have described this pain as myalgia, indurated headache, nodular headache, muscular headache and muscular rheumatism. These headaches simulate either the chronic or the intermittent type of atypical neuralgia proper and may be associated with vertigo, vomiting and earache. The muscles of the neck are hard and hypertonic, occasionally they may be indurated. The sternoclavicular and acromioclavicular joints and the cervical vertebrae may be the source of arthritis. The muscles that become involved are the sternocleidomastoid, the trapezius and the splenius capitis. Frequently local pain exists over the sternoclavicular joint and the sternocleidomastoid attachment, as well as over the superior oblique and the temporal muscle. The occipital nerve may be tender, the tactile sense becomes much exaggerated, and the muscles themselves may feel thicker than normal. Massage of these muscles, on an average of three times a week, is extremely beneficial. For chronic sufferers, when the acute pain has subsided, massage every two weeks for a year is indicated. Exercise, removal of the foci of infection, use of infra-red light and administration of sedatives are also of value.

Senile Neuralgia —Oppenheim² discussed a case of senile neuralgia in which the pain, he concluded, was due to osseous changes in the edentulous jaw, causing compression of the nerve endings. Whether or not this explanation is correct, resection of the alveolus does not always cure the pain. Glossodynia, another name used by Oppenheim, suggests a similar condition in the tongue. There is a burning, prickling sensation of the tongue, unilateral or bilateral, with or without a pronounced fear of cancer. Usually this disease occurs in elderly women. Whether the sensation is the result of the fear or whether the fear is secondary to the sensation is hard to determine. It is more likely that the sensation comes first and that its interpretation by the patient as an early sign of malignant disease is secondary. As to the cause of these unpleasant sensations in senile persons there is room for much speculation, certainly one should interpret them in terms of the mental and physical state of the patient. Arteriosclerosis and vascular insufficiency affecting the nerve endings seem the most plausible cause, the lesion,

21 Peritz, G. Neuralgie, Myalgie, Berl klin Wchnschr **44** 952, 1907

22 Halle. Die Bedeutung der Myalgien für Diagnostik und Therapie in der Rhino-Otologie, Verhandl d Gesellsch deutsch Hals- u Nasen- u Ohrenärzte, 1921, p 423

23 Mithoefer, W. Hypertonic Muscles of the Neck as a Cause of Headache, Ann Otol, Rhin & Laryng **43** 67 (March) 1934

however, may be higher in the brain stem, or the symptoms may be the first sign of progressive mental deterioration. The same types of sensation are felt in other parts of the body, notably in the extremities of arteriosclerotic patients. Oppenheim described a case of senile neuritis with definite signs of impairment of function of the peripheral nerves, in such a case the lesion is supposed to be thickening and obstruction of the vasa nervorum with overgrowth of the connective tissue of the nerves.

ATYPICAL NEURALGIA PRODUCED BY SYSTEMIC DISEASES

Allergy—Allergic headaches, classified by many as true migraine, closely simulate in many instances the pains of atypical neuralgia. That allergy can cause these pains is an established fact. In my own experience, I have known 2 patients with true atypical neuralgia to be relieved of their symptoms when they refrained from eating the foods to which they were sensitive (Rowe,²⁴ Balyeat and Brittain,²⁵ Vaughan²⁶).

Endocrine Disturbance—Riley,²⁷ in a review of migraine, and Glass²⁸ reported success in the treatment of headache with endocrine preparations. These patients revealed an abnormal ratio of estrogenic and gonadotropic substances as measured by their excretion in the urine. Case histories showed that the seizure was preceded by an increased output of gonadotropic substance, and the observers were actually able to induce headaches in these women by the injection of gonadotropic substance. Glass, in the study of 10 cases, showed a reversal of the normal ratio in the direction of increased output of gonadotropic substance and decreased output of estrogen. Estrogenic therapy suppressed the output of the gonadotropic substance, producing relief of symptoms in 80 per cent of the cases. In the other cases, administration of gonadotropic substance either gave no relief or intensified the symptoms.

Psychoneurosis—Most of the patients with atypical neuralgia have a definite associated neurosis. In the majority of cases this neurosis is caused by persistence of the pain. This continuous gnawing, exasperating pain is sufficient to bring about nervous manifestations. For this reason, it has always been helpful to administer sedatives and to have the patients remain occupied and take a certain amount of physical

24 Rowe, A. H. Food Allergy. Its Manifestations, Diagnosis and Treatment, J. A. M. A. **91** 1623 (Nov. 24) 1928.

25 Balyeat, R. M., and Brittain, F. L. Allergic Migraine, Am. J. M. Sc. **180** 212 (Aug.) 1930.

26 Vaughan, W. T. An Analysis of the Allergic Factor in Recurrent Paroxysmal Headaches, J. Allergy **6** 365 (May) 1935.

27 Riley, H. A. Migraine, Bull. Neurol. Inst. New York **2** 429 (Nov.) 1932.

28 Glass, S. J. Migraine and Ovarian Deficiency, Endocrinology **20** 333 (May) 1936.

exercise. However, there is no question that in some cases a true psychoneurosis exists which accounts for the entire picture. The patients have as a rule a variable form of atypical neuralgia, for they seem never to tell the same story. A psychiatric study of these patients always reveals definite reasons for their generalized nervous manifestations. Their condition differs distinctly from the atypical neuralgia with a secondary neurosis, and their pain should not be confused with the neurotic manifestations of patients with secondary neuroses. Oppenheim called attention to pains and unpleasant sensations in the jaws or the tongue of elderly persons as an early sign of a senile psychosis with somatic delusions. In such cases profound depression frequently develops, and these somatic delusions may be misinterpreted as atypical neuralgia before the delusional state becomes manifest.

ATYPICAL FACIAL NEURALGIA DUE TO LESIONS OF THE HEAD, CHEST AND ABDOMEN

White,²⁹ in a personal communication, wrote of a patient who had previously been relieved of atypical neuralgia by sympathectomy. The pain had recurred and was again relieved by the removal by Penfield of a calcified cerebral mass. Refractive errors and infections of the eye may occasionally produce the picture of atypical neuralgia. Three such cases occurred in my series. Involvement of the mastoid and thrombosis of the lateral or the cavernous sinus may also produce this characteristic pain. Three such cases came under my observation. Deep-seated infections of the face may also give a similar picture. This occurred in 2 cases. Little difficulty should be entailed in making the diagnosis of this kind of neuralgia. The pain is usually acute and not of long standing, the temperature is high, and evidence of the associated disease is clear. In cases of deep-seated facial abscess, however, the pain may persist from four to seven days before evidence of local infection presents itself.

Dental sepsis occasionally produces the same picture. Six cases in my series represented this type of origin. One must be exceedingly cautious, however, in deciding on dental involvement as the cause of the pain. As I have previously stated, too many teeth have been removed uselessly, without relief of pain, and only in those cases in which one is certain of the presence of ill fitting bridges, tight fillings or abscessed teeth should one consider the extraction of teeth or the removal of bridges. In 1 patient the nasal septum was markedly deviated, and a spur was situated in the sphenopalatine region. Straightening of the septum and removal of the spur relieved the patient of pain.

29 White, J. Personal communications to the author, 1938.

In a number of cases thoracic and abdominal, as well as pelvic, lesions were responsible for neuralgia Lapinsky,³⁰ Fay³¹ (1932) and Pottenger³¹ have called attention to this syndrome

PHYSIOLOGY

The pain of atypical neuralgia and that of migraine have many similar characteristics In each the pain is not of the acute type associated with neuralgias of the peripheral nerves, such as trigeminal and glossopharyngeal neuralgia, but is more like the pain associated with vascular disease It is a burning, pressing, aching, annoying, discomforting pain That the blood vessels are sensitive to pain is a well known fact based on clinical and experimental studies The distribution of atypical neuralgia is not identical with that of any cranial nerve or of any combination of nerves, but does follow to a certain degree the course of the vasculature of the head (see fig 1) The blood vessels, without doubt, act as conduits by which sensory nerves are carried to the various parts All these nerves probably include afferent components of cerebrospinal nerves

Moore, Moore and Singleton³² have demonstrated the chemical stimulation of nerve endings for pain in small blood vessels, while the sensitivity of blood vessels has been reviewed in detail by Kuntz³³ and the innervation of the blood vessels has been adequately discussed by Woollard³⁴

The afferent impulses of pain originate in the walls of blood vessels, and nonencapsulated sensory endings are known to occur in the adventitia Spiegel and Wassermann observed that slight distention of the ascending aorta elicited pain, while Odermatt demonstrated that pain may be elicited by the distention of arteries of any caliber Bazett and McGlone³⁵ showed that simple puncture of the wall of an artery is very painful They personally have informed me that such pain closely simulated that of atypical neuralgia and was of a dull, aching,

30 Lapinsky, M Visceral bedingte Genicksteifigkeit und Gleichgewichtsstörung, *Med Welt* **1** 1306 (Oct) 1927

31 Pottenger, F M Disturbances in the Vegetative System in Diseases of the Lungs and Visceral Pleura, *A Research Nerv & Ment Dis*, *Proc* **9** 587, 1930

32 Moore, R M, Moore, R E, and Singleton, A O, Jr Experiments on the Chemical Stimulation of Pain-Endings Associated with Small Blood-Vessels, *Am J Physiol* **107** 594 (March) 1934

33 Kuntz, A *Autonomic Nervous System*, ed 2, Philadelphia, Lea & Febiger, 1937, p 145

34 Woollard, H H The Innervation of Blood Vessels, *Heart* **13** 319 (Dec) 1926

35 Bazett, H C, and McGlone, B Note on the Pain Sensations Which Accompany Deep Punctures, *Brain* **51** 18 (March) 1928

unbearable quality, frequently accompanied by sweating, sensation of warmth or cold, faintness or even loss of consciousness. Introduction of barium chloride and various manipulations of the blood vessels produced pain. Clinical conditions of the arteries, such as ischemia, Raynaud's disease, angina pectoris and embolism, give further proof that the arteries are sensitive to pain. It has long been known among neurosurgeons that in an operation with local anesthesia pressure on the middle meningeal artery produces pain.

Penfield³⁶ has demonstrated that the dural sinuses are sensitive to pressure, traction, heat and electrical stimulation. Pull exerted on the falx and tentorium produced pain, but Penfield said he believed that this pain was secondary to sinusal response. A cicatrix was generally associated with great increase in sensitivity of the adjacent dura. The cerebral veins were usually not sensitive, though the large vein of the sylvian fissure occasionally was sensitive to electrical stimulation, this sensitivity, however, could be due to escape of current to the larger arteries of the fissure. The large cerebral veins were also sensitive at times. Pacchionian granulations were sensitive, and electrical stimulation of the middle cerebral artery produced pain. The dura was sensitive only over the middle meningeal vessel. The pain from the cerebral vessels was referred about the temples and the head and deep into the eye, but not to the face, and was of the nature of pressure or of sharp pain.

Franklin,³⁷ in his monograph on veins, further indicated the sensitivity of the veins and called attention to the fact that Goobler, in 1894, noted that a peculiar sensation arose during contraction in response to mechanical stimulation of the veins on the dorsum of the hand. The probable pathways of the afferent impulses of the veins are through the vagus nerve.

All these facts point not only to the vascular origin of these peculiar pains but also to the difficulties of intercepting them. Chorobski and Penfield³⁸ noted that complete removal of all the sympathetic nerve fibers which enter the cranial cavity on the carotid and the vertebral arteries does not appreciably reduce the number of normal intracranial perivascular nerve fibers. The authors stated that occasional branches to the pia from other cranial nerves need further investigation, and it became evident to them that denervation of cerebral blood vessels is

36 Penfield, W. A Contribution to the Mechanism of Intracranial Pain, *A Research Nerv & Ment Dis*, Proc **15** 399, 1934.

37 Franklin, K. J. A Monograph on Veins, Springfield, Ill., Charles C Thomas, Publisher, 1937.

38 Chorobski, J., and Penfield, W. Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on the Pia and Intracerebral Vascular Plexus, *Arch Neurol & Psychiat* **28** 1257 (Dec.) 1932.

without doubt a surgical impossibility. They suggested that the parasympathetic pathway is interrupted by synapses, with scattered ganglion cells, just before reaching the internal carotid artery, and that the cervical portion of the sympathetic chain, which has been thought to have its postganglionic stations in the superior cervical sympathetic ganglion, may also be interrupted by the scattered ganglion cells along the course of the internal carotid and cerebral arteries.

The means of conduction of pain of atypical neuralgia is still a matter of some doubt. In all likelihood the atypical neuralgias represent numerous types of production of pain. There is no question that this pain is carried over the carotid and vertebral arteries, as well as over the vertebral veins and the branches of the jugular vein and the dural sinuses. It is even possible to consider some of these types of pain as of central origin.

Langley and Gaskell concluded that the sympathetic system is a purely motor system and that the sympathetic nerves carry no sensory fibers of their own. Stohr's conception that the nonmyelinated fibers are functionally the same as the myelinated fibers finds confirmation in the experimental work of Allen, and also in that of Windle, who found that the pain tracts for the teeth are formed partly of nonmyelinated and poorly myelinated fibers. Morphologically, it is definitely established that the rami communicantes contain myelinated and nonmyelinated fibers which go through the anterior and posterior roots of the ganglionated cord. The number of myelinated fibers a nerve possesses is no indication of whether it belongs to the sympathetic or to the cerebrospinal system. Sensory fibers must also be present in the rami communicantes since sensory endings are present in the area of distribution of the sympathetic system, and since after section of an area of the sympathetic system triglycolysis is observed in cells of the associated spinal ganglion.

Helson,³⁹ who stated a firm belief that the afferent fibers actually are part of the sympathetic system, gave the following reasons to support his view:

Although I should not want to negate the possibility that contraction or dilatation of the blood vessels stimulates somatic nerve receptors in the blood vessels, it seems to me probable that the autonomic nervous system has afferent fibers truly belonging to it. It may be only a matter of definition, but definitions are extremely important. The article by Foerster and his colleagues referred to in my study with Frazier cites much evidence in support of autonomic afferent fibers, and there are many other articles in which the same position is taken. One German writer asserted that all pain is mediated by the autonomic nervous system, an

39 Helson, H. Personal communication to the author, Sept 7, 1938, *The Part Played by the Sympathetic System as an Afferent Mechanism in the Region of the Trigemini*, *Brain* **55** 114 (March) 1932.

extreme position I should not take. Ranson, several years ago, mapped the number of spots for pressure, pain, warmth and cold sensation on several parts of the body and then counted the number of fibers in the area. He found enough large fibers (8 to 16 microns) to account for pressure sense, enough medium fibers (5 to 8 microns) for temperature sense, but not enough small fibers (1 to 5 microns) for pain sense, unless he included the unmyelinated fibers (under 1 micron), in which case he had just enough. Now the usual assumption is that the unmyelinated fibers in any peripheral bundle belong to the autonomic nervous system, the post ganglionic fibers of which are unmyelinated. The longer latent period and the slower arousal of pain sensation argue for fibers of slow conduction (hence of small diameter). Perhaps the solution simply requires histologic examination to determine the cells of origin of these smallest, unmyelinated fibers. Recent experimental work on antidromic impulses and the newer views of synaptic action make it seem less improbable that the autonomic nervous system is afferent as well as efferent. Recent emphasis on the thalamus as both the seat of emotions and an autonomic center also lends support to this view. In any case, I believe that the peripheral afferent system masks the autonomic afferent system in the normal, intact organism and so the latter system does not normally function primarily as an afferent conductor. Evidence from the chronaxias of normal versus deafferented skin supports this theory.

Helson stated he would gladly revise his opinion if further evidence were available. This view of Helson's, however, is not shared by the majority of clinicians and is not in accord with accepted opinions.

It is also believed that the sensory neuron actually conducts the pain sense, but runs within the sympathetic trunk. Indirectly the sympathetic system may be responsible for the pain when, by means of vasoconstriction, a metabolite is produced which causes painful stimulation of the cutaneous sensory nerve. Referred pain, according to the McKenzie-Ross theory, may also be a causative factor. Some form of sensation, not true pain, travels up the splanchnic and other visceral nerves as far as the posterior horn. There the bombardment of the visceral impulses sets up an irritative focus. The threshold for the somatic impulses, which are constantly entering the same segment from the periphery of the body, is diminished. The nerve cells act according to their function. When such stimuli from the splanchnic nerves and from other visceral nerves bombard these cells, pain consequently arises and is referred to the peripheral distribution of the nerve stimulated. Sweating, goose flesh and other manifestations must be due to reflexes through arcs made up of visceral afferent and visceral efferent chains.

Considerable study has been carried out in order to determine the pathways by which atypical neuralgic pains travel. If these pathways could be accurately located, the problem of atypical neuralgia would be solved because interception of these pathways by surgical measures would relieve the pain in the same manner as section of the sensory root relieves trigeminal neuralgia. Unfortunately, the pathways for

pains of atypical neuralgia are not as simple as those of trigeminal neuralgia, and the operations which would necessarily interrupt them would have to be unusually extensive, even then, the patient would not be assured of entire relief

Fay^{3b} (1932), after reviewing the various combinations of sensory, sympathetic, vagal and vascular nerve sheath resections and analyzing the results (assisted by a process of negative elimination), indicated the existence of three distinct mechanisms for pain transmission in the structure of the head, face and neck (1) the trigeminal and cervical branches for superficial pain, (2) the sensory branches and connections of the vagus nerve for deep pain, and (3) along the arterial tree through the carotid sheath to the cervical and thoracic portions of the cord for tenderness and deep pain. Fay's opinion was confirmed by Kuntz⁴⁰ as the result of experimental anatomic studies on cats. Kuntz stated that after degeneration of the divided nerve fibers had taken place after extirpation of the superior cervical sympathetic and nodose ganglions in his experiments, sections through the common internal and external carotid arteries and the nerves closely associated with them still revealed intact nerve fibers. Marchi preparations of the common and internal carotid arteries made after section of the roots of the upper four thoracic nerves just distal to the spinal ganglions revealed degenerated myelinated fibers in considerable numbers. On the basis of these observations, he said, it is evident that afferent components of the upper thoracic nerves join the plexus on the common carotid artery and extend cephalad along the internal and probably also along the external carotid artery. The presence of myelin degeneration in Marchi preparations of the nasal and nasociliary nerves after section of the roots of the upper four thoracic nerves (Christensen 1934) indicates that some of the afferent components of the thoracic nerves which extend into the cephalic region reach the orbit and the nasal mucosa. After degeneration of the divided fibers following extirpation of the entire cervical sympathetic trunk, including the superior cervical ganglion, but with the vagus nerve left intact, sections of the internal and external carotid arteries and the nerves associated with them revealed numerous intact fibers obviously of vagus origin. These fibers probably were afferent components of the vagus with their cells of origin in the nodose ganglion. The afferent spinal nerve components, which extend into the cephalic region, probably are not primarily pain-conducting fibers. Those which underwent myelin degen-

40 Kuntz, A. Pathways Involved in Pains of Nasal and Paranasal Origin, Referred to the Lower Cervical and Upper Thoracic Segments and the Upper Extremity, *Ann Otol, Rhin & Laryng* **45** 394 (June) 1936, Nerve Fibers of Spinal and Vagus Origin Associated with Cephalic Sympathetic Nerves, *ibid* **43** 50 (March) 1934

eration in the plexuses on the common and internal carotid arteries after section of the nerve roots, as observed in the Marchi preparations, were mainly fibers of larger caliber than the spinal nerve fibers which are known to mediate pain. Mild electrical stimulation of the plexus on the common carotid artery experimentally did not elicit pain reactions, but resulted in reflex responses in the lower cervical and upper thoracic segments and particularly in the forelimb. The vagus components which join the plexuses in the internal and external carotid arteries are mainly fibers of small caliber, many of which are either unmyelinated or only thinly myelinated. Many of these probably are fibers which normally mediate pain. The existence of afferent fibers of spinal nerve origin along the carotid arteries has been verified by Laisell.

Davis and Pollock,⁴¹ on the basis of experimental work, demonstrated that stimulation of the superior cervical sympathetic ganglion produced an effect that was carried by way of the postganglionic efferent fibers to the structures innervated by the sympathetic fibers. These efferent impulses then produced on the skin and other structures an effect the exact nature of which they were unable to state. They expressed the belief that the effect was linked with the sympathetic innervation of the blood vessels and that a metabolite was liberated which stimulates the ordinary sensory nerve endings of the fifth nerve. These impulses were then transmitted centrally and were recognized as pain. The part that the afferent impulses through autonomic nerves play in the production of pain must still be regarded as problematic. Kuntz asserted that it is no longer necessary to assume afferent conduction in autonomic fibers. In all the conditions referred to in this paper afferent fibers are available. One cannot deny the painful character of arterial spasm, but experimental studies show that it must be discounted. On the other hand, clinical data indicate that vasomotor phenomena which were associated with atypical neuralgia in this series of cases and in the cases reported by Brickner and Riley were relieved by medication directed toward the autonomic system. In 50 per cent of the cases reported by Beerman and me, there were sympathetic phenomena. The problem is still one to be solved, and as experimental work is further carried out its clinical application to atypical neuralgia will without doubt eventually bring about the relief of the pain.

TREATMENT

In the treatment of atypical neuralgia, every effort should be made to eliminate the secondary factors which may bring about the pain. In cases in which the pain has been present for a short time the results

41 Davis, L., and Pollock, L. J. The Role of the Sympathetic System in the Production of Pain in the Head, *Arch. Neurol. & Psychiat.* **27**: 282 (Feb.) 1932.

of treatment are far better than in those in which the pain has persisted over a long period. In cases of the early form the cause is usually established. Therapy should be ultraconservative, particularly in regard to surgical measures, for in many cases the condition is made worse rather than improved if the wrong operative procedures are carried out.

In dealing with cases of primary atypical neuralgia for which one has been unable to find a definite cause, treatment must be directed either by medical or by surgical methods toward the nerves responsible for the pain. Many of the patients have an associated psychoneurosis which is brought on by the persistent and nagging character of the pain. Occasionally, however, one does find patients whose psychoneurosis is the causative factor, but in the series under my observation there were only a few such persons. In such instances the treatment must be directed toward the existing neurosis. It is apparent that some of these patients have a very low threshold for pain, so that they greatly magnify the pain they have. The medical treatment consists of the use of the choline compounds. Simonart⁴² concluded

Of all the compounds investigated the acetyl ester of β -methyl choline appears actually to offer the greatest possibility of clinical usefulness, since it is approximately as potent as acetyl choline in lowering blood pressure when given intravenously, it has no demonstrable nicotinic action on the circulation, and it is so much more stable than acetyl choline that it is effectively absorbed from the intestinal tract and is much more potent than acetyl choline when injected subcutaneously.

Two of my patients have been relieved by acetylbetamethylcholine; one, a woman who became addicted to narcotics because of this pain, has been relieved for seven years, the other, for two years. McLean⁴³ reported 2 cases in which relief was obtained by acetylbetamethylcholine chloride (mecholy)l. In addition to administration of the choline compound, therapeutic attempts should be directed to the use of other drugs which stimulate the parasympathetic and the sympathetic system, such as epinephrine, ergotoxine, amyl nitrite, physostigmine and atropine. One of my patients, with a "trigeminal ghost" in the eye in which the pain was definitely localized, received relief from the pain for several months by instillation of atropine into the eye. Four of my patients were relieved by the inhalation of trichloroethylene. Abbott⁴⁴ reported the relief of 10 patients by such inhalations.

42 Simonart, A. On the Action of Certain Derivatives of Choline, *J. Pharmacol. & Exper. Therap.* **46** 157, 1932.

43 McLean, A. J. Personal communication to the author.

44 Abbott, W. D. Personal communication to the author.

Fay⁴⁵ stated that he obtained relief by a full course of applications of heat to the base of the neck

Fincher,⁹⁰ in discussing Wilson's paper, told of the work of Dr J D Thomson, who produced relief in cases of atypical neuralgia

Using a solution of magnesium sulphate and magnesium borate, in glycerin, he places a small tampon in the auditory canal down against the drum membrane Over 50 per cent of his results have been noted in three or four hours afterward Some of these patients have gone as long as five to six months before it was necessary to change the tampon He has followed these cases for several years, without recording his results

Flothow⁴⁶ stated he was not able to tell whether the injection actually gives relief or whether the relief is due to a psychic effect Nevertheless, he has had some success with this method in 4 cases In all his cases the pain was not continuous, but intermittent The middle and inferior cervical ganglions and the first and second thoracic ganglions were removed In 1 case the pain was relieved for a long time In 2 other cases there was associated tic douloureux, which was relieved by injection of alcohol In the fourth case the pain was relieved, but the patient died of postoperative pneumonia McLean reported a case of atypical neuralgia combined with true trigeminal neuralgia in which relief was given by a diagnostic procaine block of the cervical portion of the sympathetic chain It is difficult for one to understand how a temporary block, such as is obtained with procaine, could relieve such a condition unless it was purely functional

White²⁹ relieved 1 patient by surgical excision of the inferior cervical and upper two thoracic ganglions The pain remained absent for five years and then returned Later, as I have previously mentioned, this patient was relieved by excision of a calcified area in the falx

In a second case of White's, it was necessary to resect the first and second thoracic ganglions, the inferior cervical sympathetic ganglions and the common carotid artery Reichert⁴⁷ reported 5 cases of a combination of trifacial neuralgia and atypical neuralgia Resection of the fifth root relieved the tic, and in 3 cases of atypical neuralgia the pain was relieved by injection of alcohol into the seventh cervical ganglion and the first and second thoracic ganglions In the other 2 cases relief was not obtained

Grant⁹⁸ obtained relief in 1 case of atypical neuralgia by the removal of the stellate ganglion Abbott secured relief in 4 cases Dandy⁴⁸

45 Fay, T Personal communication to the author

46 Flothow, P G Personal communications to the author

47 Reichert, F L Personal communication to the author

48 Dandy, W D Personal communication to the author

reported on the treatment of hemicrania by removal of the inferior cervical and first thoracic sympathetic ganglions in 2 cases. Penfield relieved this pain in 2 cases by the following procedure. He removed the superior cervical sympathetic ganglion, decalcified the carotid artery, excised the upper pole of the stellate ganglion and the plexus on the vertebral artery and then cut the upper divisions of the fifth sensory root. The patient has been free from pain for three years. In the second case the superior cervical sympathetic ganglion was removed and periaarterial sympathectomy was performed on the carotid artery, together with a subtotal resection of the sensory root of the fifth cranial nerve. The plexus on the vertebral artery was not removed, and consequently pain remained in the posterior part of the left side of the head and neck. Multiple operations have been carried out by Braeucker,^{9a} who reported relief of atypical neuralgia, which he called "pseudotrigeminal neuralgia." He extirpated the gasserian ganglion and removed the sphenopalatine ganglion with all its branches, as well as the first to the fourth cervical nerves, together with the ramus of the external carotid nerve, which come largely from the superior cervical ganglion and the hypoglossal nerve. The pain in the upper jaw, with radiations over the face, head, neck and shoulder disappeared. Fay, in order to determine the sensory tracts of the head, and also to offer some relief in cases of atypical neuralgia, has operated on the occipital, glossopharyngeal, hypoglossal and vagus nerves. He has concluded, however, as recorded in a personal communication, that these operations are too formidable for therapeutic measures, and consequently he has not performed any for the last ten years.

From these observations, it is apparent that some patients with atypical neuralgia can be relieved by operations directed toward the sympathetic system. Before operation is resorted to, however, all the various therapeutic measures suggested for the secondary neuralgias should be tried. If these prove unsuccessful, there is a possibility that the patient can be relieved by surgical procedures on the sympathetic system mentioned in the preceding paragraphs. Operations on the sympathetic system and injection of alcohol should not be carried out unless a diagnostic procaine block has been employed. If alcohol is injected, great difficulty will be encountered in later surgical measures because of the mass of adhesions that form about the site of the injections.

If an operation is to be performed, it seems reasonable to assume that in some cases removal of the stellate ganglion and of the first and second thoracic ganglions is sufficient to relieve the pain. However, if removal of these ganglions does not relieve the pain, injection of alcohol into the trigeminal nerve may be performed. This injection

should be made because isolated ganglion cells within the leptomeninges or an isolated ganglion cell on the carotid artery within the skull may react within its own area of distribution and the pain impulse be carried to consciousness along the route of the trigeminal nerve or because it is possible that efficient pain impulses may travel along the fifth nerve, producing a metabolite which stimulates the general cutaneous ending. Penfield did not advise the removal of the stellate ganglion if all the connections with the head are interrupted by excising both the superior cervical sympathetic ganglion from the carotid artery and the saddle-shaped ganglionic extension along the vertebral artery. Further time and added clinical experience are necessary to evaluate satisfactorily the results of these surgical procedures, but at least a logical solution of this problem is gradually being found.

SUMMARY

Though the term "atypical neuralgia" is not particularly good it is no less explanatory than "migraine." The close relationship of the clinical picture of atypical neuralgia to that of migraine is apparent, and when a new name is decided on it should incorporate both clinical entities. Atypical neuralgia has been described in the literature under a number of terms, and in this paper an effort has been made to correlate the various clinical and pathologic entities which may produce this syndrome. One should no longer be baffled in the attempt to find a remedy for this syndrome, but should make every effort to find the secondary causes, to utilize the various conservative medical treatments suggested and, finally, to rely on test nerve blocks before attempting the various surgical procedures.

One cannot overemphasize the need for extreme caution in carrying out operative procedures on such structures as the teeth and sinuses, unless the certainty of a pathologic process in these regions actually exists. If one is too radical in such operative work, more harm than good will result and the patient will be far worse than before operation. Each patient should be looked on as a diagnostic problem, and no procedure should be carried out without a long study.

GASTROSCOPY AND THE PHYTOBEZOAR

REPORT OF A CASE OF DIOSPYROBEZOAR

DONOVAN C BROWNE, M D

AND

GORDON McHARDY, M D

NEW ORLEANS

Phytobezoars are sufficiently rare to justify our being stimulated to publication of a case recently observed. When DeBakey and Ochsner¹ completed their critical analysis of the literature on 311 intragastric foreign bodies, they were able to report only 126 instances of phytobezoar.

Bezoars have always been of considerable interest and have from antiquity been prized by their discoverers. In the earlier days they were valued as charms and as curative agents. Today they serve as excellent exhibits for medical meetings. Numerous manuscripts reviewing their history, method of formation, character, diagnosis and treatment have appeared in the literature.²

Since these phases have been studied and reported on adequately, we shall confine our discussion to the most recent advance in the study of bezoars, the use of the gastroscope. It was first reported in 1936 by Moersch,³ who viewed a phytobezoar in situ with the flexible gastroscope.

Moersch's patient had been gastrotomized for removal of a bezoar in 1935, with the surprising result that the roentgenologic findings could not be confirmed. When, in 1936, the roentgenogram again indicated the presence of a bezoar, the patient refused to have an operation until a gastroscopic examination had convinced him of the validity of the established diagnosis. A phytobezoar was successfully removed. This case illustrates the definite value of gastroscopy as an added diagnostic procedure.

From the Department of Medicine, School of Medicine, Tulane University, and the Gastroenterology Clinic, Touro Infirmary.

1 DeBakey, M., and Ochsner, A. Bezoars and Concretions, *Surgery* **4** 934, 1938, **5** 132, 1939.

2 (a) Matas, R. Hairballs of the Stomach, *Tr. South Surg. & Gynec. Assn.* **26** 603, 1914. (b) Maes, U. Bezoars, *Ann. Surg.* **88** 685, 1928.

3 Moersch, H. J., and Walters, W. Phytobezoar with Visualization by Means of Gastroscopy, *Am. J. Digest. Dis. & Nutrition* **3** 15, 1936.

Ruffin and Reeves⁴ reported a case in which the roentgenologist could state only that there was an indefinite irregularity along the lesser curvature of the stomach, with a filling defect near the pylorus, then endoscopic study revealed a mobile body identified as a bezoar. Surgical removal was resorted to, and laboratory study showed the specimen to be a phytobezoar.

Patterson and Rouse⁵ viewed a phytobezoar and had their gastroscopic study verified at operation.

None of these observers were able to demonstrate an associated ulceration by gastroscopic examination, and from their reports one concludes that in no case was ulceration found by the surgeon.

Aside from phytobezoars, Benedict⁶ has studied a plum seed and a prune seed in the stomach. Segal⁷ had the unusual experience of seeing a large gallstone penetrating the gastric wall from an adherent gallbladder. This stone was nonopaque to roentgen rays and therefore was not seen on roentgenologic study. In a gastroscopic study Rouse and Patterson⁵ found multiple foreign bodies which had been missed by roentgenogram, they were thought to be phytobezoars but on exploratory operation were found to be four large greenish bile-stained tablets. A chemical study showed them to be 10 grain tablets of magnesium carbonate, their retention was due to partial pyloric obstructions and their intact state probably to an existing achlorhydria.

A phytobezoar seen gastroscopically appears as a large smooth ovoid mass of dark color, glistening because of its mucous coating and usually freely movable. One would expect to find an associated gastric ulceration in 23 per cent of the cases, with other evidence of mucosal irritation.

REPORT OF CASE

History—T. E. S., a 69 year old white man, first seen on March 6, 1939, gave a history that in September 1938, while investigating a historic cemetery, he happened on a persimmon tree. On an empty stomach he ate a generous quantity of the ripe fruit. He took home a supply, from which he ate, a half-hour before breakfast, on three successive mornings. (The patient was meticulous in giving the foregoing statement.) On the fourth day he began to experience epigastric distress, a pain which started to the right of the midline and radiated across the abdomen. Subsequently this pain became postprandial, and was partially relieved by alkali and by milk. Numerous physicians were consulted, but no relief was obtained from any therapeutic regimen. In December 1938 a gastric fluoroscopic

4 Ruffin, J. M., and Reeves, R. J. The Value of Gastroscopy in the Diagnosis of Phytobezoar, *Am J Digest Dis* 5:745, 1939.

5 Patterson, C. O., and Rouse, M. O. The Clinical Use of the Flexible Gastroscope, *Texas State J Med* 39:746, 1939, personal communication to the authors.

6 Benedict, E. B. Personal communication to the authors.

7 Segal, H. Personal communication to the authors.



Fig 1—Roentgenogram showing the bezoar displaced into the upper portion of the stomach by external pressure



Fig 2—Roentgenogram, taken at the six hour stage of the gastrointestinal series, showing the bezoar with typical barium outline

examination revealed what was considered to be abnormal retention of food and barium. On the basis of the history a diagnosis of duodenal ulcer with partial pyloric obstruction was made, and the patient was put on a routine for ambulatory patients with ulcer. Obtaining no relief, the patient became progressively more apprehensive and of his own volition eliminated various foods from his diet. He lost about 10 pounds (4.5 Kg) in weight during five months. There was no history of nausea, emesis or melena.

Examination—The routine physical examination revealed senile changes, both mental and physical, a thoracotomy scar in the right lower quadrant of the thorax (from empyema drainage, 1926), basal pulmonary congestion with evidence of pleural changes at the base of the right lung, umbilical and epigastric hernias and slight hepatomegaly.



Fig. 3—Drawing showing the gastroscopic view of the bezoar.

Urinalysis gave negative results. The blood count and blood chemistry were normal, and two Wassermann tests were negative. The ascorbic acid content of the blood was 0.32 mg per hundred cubic centimeters. Gastric analysis showed the total acidity to be 78, with the free hydrochloric acid 58.

The gastrointestinal roentgenograms on March 7 revealed within the stomach an oval nonopaque mass, approximately 5 by 4.5 cm in diameter. Fluoroscopic examination showed that this barium-coated object was mobile and could be displaced by palpation from the lower portion of the corpus of the stomach well up into the cardia. Secondary ulceration on the lesser curvature in the pyloric antrum was suspected, although not definitely established. In six hours the stomach was emptied except for the barium which had collected on the walls of the intragastric mass. The opinion was expressed that a bezoar existed, although the possibility of a gastric polypus with an unusually long pedicle was considered.

Gastroscopic Examination—On March 10, a Wolfe-Schindler flexible gastroscope was passed and the interior of the stomach examined. The gastroscope was

introduced just short of the greatest depth. The pyloric antrum did not come into view, a dark mass obstructing the field. As the gastroscope was advanced, this object could be seen to move. External pressure was applied over the stomach at this time, and as the angulus was brought into view, the mass was seen to occupy a position which partially obstructed the view of the antrum. The foreign body could be studied in detail, it was grayish black, irregular in outline, glistening and covered with mucus. A brownish pool of mucus extended from the proximal margin. Sketches were made of the mass in this position. A more satisfactory view of the antrum was not possible, a careful inspection of the remainder of the stomach revealed normal mucosae except for increased vascularity on the lesser curvature at the angulus. No ulcerations were seen.



Fig 4—Photograph of the bezoar

A preoperative diagnosis of a single phytobezoar was made. In preparation for surgical treatment the patient was given generous quantities of vitamin C. Mild prostatic symptoms, which developed after he was at rest, were treated by a urologic consultant.

Operation—On March 15, 1939, with the patient under general anesthesia, a gastrotomy was performed by Dr. Alton Ochsner through a left upper paramedian incision. Preliminary exploration and palpation revealed in the lumen of the stomach a mass of rocklike consistency, which was freely movable. Examination of the other viscera revealed no abnormality. A small incision was made in the midportion of the anterior wall of the stomach at a right angle to the long axis, and the interior of the stomach was visualized, the foreign body was removed intact. No other masses were encountered. The mass had all the visible characteristics of a phytobezoar and measured 4 by 7 cm. Surgical closure was done in the usual manner.

Course—The patient's postoperative condition was good, and he seemed on the way to a successful convalescence when, on the sixth day after surgical intervention, there was a sudden onset of severe pulmonary symptoms, with a pleural rub at the base of the left lung. Subsequently, frank pneumonitis became evident over this area. Typing of the sputum revealed no specific organisms, so the patient was given sulfapyridine, supplemented by a small transfusion and other supportive measures. The need for digitalization was indicated by marked tachycardia with progressive pulmonary edema. Oxygen and stimulants were given. The patient became progressively worse and died on March 27.

Pathologic Study—The significant observations at necropsy, abstracted from the pathologist's report, were as follows. The peritoneum was smooth, glistening and grayish pink and showed no evidence of any inflammatory reaction. The spleen was somewhat enlarged. The right pleural cavity was obliterated by



Fig 5—Drawing showing the stomach as removed at autopsy, with a large ulcer on the lesser curvature at the antrum, the surrounding areas of superficial erosion are also shown.

fibrous adhesions, the left pleural cavity was partly filled with loose fibrinous adhesions. The left lung was partly surrounded by fibrinous adhesions, which were most dense around the lower lobe. Both lobes were less crepitant than normal, the lower lobe was partly consolidated. On section, an area of infarction was found in the lower lobe near the periphery, showing liquefaction. This area measured 8 cm in length and extended 4 cm into the parenchyma. The surrounding lung tissue, in both lobes, was markedly congested, showing evidence of acute inflammatory reaction. Examination of the pulmonary artery showed a rather large thrombus, which partly occluded the vessel, many of the smaller blood vessels were filled with thrombi.

There was a recent scar, 5 cm long, in the midportion of the stomach, on the anterior surface, it had completely healed, with no gastric distortion. When

the stomach was opened, there was seen on the lesser curvature, 3 cm from the pyloric valve, an ulcer 2.5 cm in diameter, which was free of gross evidence of acute inflammatory reaction. There was no evidence of bleeding. The edge of the ulcer was not indurated, the lesion was 0.5 cm in depth and was distinctly punched out.

The bezoar was truly a phytobezoar. Ovoid in shape, it measured 4 by 7 cm immediately on removal but subsequently shrank, as is seen in figure 4. The surface was smooth and black. The mass was hard, firm and compact on removal, but after drying it became friable and crumbled readily. Sectioning revealed a heterogeneous structure of brownish color, consisting of gummy material interspersed with cellulose fibers, skins and seeds.

COMMENT

While earlier writings of Chevalier Jackson and others contained references to foreign bodies viewed gastroscoically, no mention was made of bezoars until the report of Moersch, in which the more practical flexible gastroscope was given credit for his ability to study a phytobezoar in situ. The case we are reporting is a typical instance of phytobezoar, and our observations correspond with those previously reported. From the study of the literature there is evidence that bezoars form more readily in the empty stomach in which there is adequate acidity. Secondary ulceration along the lesser curvature was demonstrated by the roentgenologist and the pathologist but was not found by the gastroscoicist or by the surgeon. As far as we can determine, this is the one hundred and twenty-eighth case of phytobezoar to be published, it is the fourth case in which gastroscopic studies were carried out.

The unfortunate death of the patient, due to pneumonitis superimposed on infarction, has made available for the literature a completely studied case of phytobezoar. As yet, operative removal is the only rational therapeutic procedure. At the present time we have no additional information to offer as to the formation of these bodies. Search for a possible means of dissolving them has, of course, been stimulated, but our efforts in this direction have not met with sufficient success to be of practical value.

We favor the term diospyrobezoar, offered by DeBakey for this type of phytobezoar (Diospyron being the generic name for the wild persimmon).

SUMMARY

Study of the phytobezoar is a relatively new achievement for the flexible gastroscope of Wolfe and Schindler. The use of this instrument may revolutionize time-honored therapeutic principles in the treatment of bezoars as well as of all other intragastric disease, because it makes accurate diagnosis possible and the results of therapy may be checked by direct vision.

RENAL CALCIFICATION ACCOMPANYING PYLORIC AND HIGH INTESTINAL OBSTRUCTION

HARRY MARTZ, M D

BROOKLYN

The purpose of this paper is to call attention to a not infrequent and often overlooked pathologic state occurring in patients subjected to a loss of gastric or high intestinal secretions over a long period. In medical and surgical wards such patients are frequently seen presenting symptoms of pyloric or high intestinal obstruction or being subjected to continuous gastric or intestinal drainage for the alleviation of distention and vomiting. The alarming clinical picture these patients present is frequently overlooked, and effective treatment of the condition is too often lacking. The patients, therefore, are permitted to succumb to a chemical acid-base imbalance, with its accompanying impaired renal function. At autopsy, they are often found to have extensive and apparently irreparable renal calcification. The early institution of proper therapy in such cases might often forestall this outcome, for the restoration of a proper chemical balance might restore or markedly improve the function of the kidneys. It is with the aim of calling attention to the rational form of therapy for these patients, and of emphasizing the modus operandi of this form of damage to the kidneys, that I present a short description of calcium metabolism and several cases of this type of renal lesion.

HISTORY

The first cases of renal calcification associated with prolonged vomiting, secondary to pyloric stenosis, were described by Nazari¹ in 1904. He studied 2 fatal cases of gastric tetany which developed "over the course of a few days," in both of which autopsy showed calcareous deposition in the tubules of the kidneys, especially in the convoluted tubules and in the ascending limb of Henle's loop. Nazari interpreted these changes as entirely of toxic origin, though he could not recover the noxious element in the blood.

In 1923, Brown, Eusterman, Hartman and Rowntree² reported 11 cases of "toxic nephritis" with evidences of renal insufficiency occurring

From the Surgical Service and Department of Pathology, Cumberland Hospital

1 Nazari, A. Renal Changes in Gastric Tetany, *Policlinico (sez. med.)* **11** 146, 1904

2 Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany, *Arch. Int. Med.* **32** 425 (Sept.) 1923

as the result of organic obstruction of the pylorus or of the duodenum. In 6 of these cases death occurred, and postmortem examination of the kidneys revealed severe "toxic nephritis," with tubular degeneration but no changes in the glomeruli. In 5 of these 6 cases deposits of calcium were found in the tubular epithelium, which the authors attributed to the previous administration of calcium, as a therapeutic measure. They stated, however, that Bowler had been unable to produce toxic effects on the kidneys experimentally by the administration of excessive doses of calcium chloride. In all their cases they observed an increase in the carbon dioxide-combining power of the blood as well as nonprotein nitrogen.

In 1924, Zeman, Friedman and Mann³ reported 4 cases of pyloric or high duodenal obstruction with vomiting, in which degeneration and calcification were present in the cells of the convoluted tubules of the kidney, a condition which they termed "toxic degenerative nephrosis." They did not observe "nephritis," or an inflammatory lesion. In 2 of these cases there was gastric tetany. Three of the 4 patients had received calcium salts, but the authors stated that this had no relation to the existence of renal lesions. They found no deposition of calcium in other organs, such as occurs in cases of metastatic calcification and they were unable to explain the mechanism of occurrence of the calcification of the kidney. They then tied off the pylorus in 13 cats and sustained the animals by subcutaneous injection of 10 per cent dextrose three times a day, and were able to produce identical renal changes in all the animals. These changes consisted of diffuse tubular degeneration and calcification of the convoluted tubules and were seen as early as forty-eight hours after operation. In all these animals there were a rise in the carbon dioxide-combining power and in nonprotein nitrogen and a fall in chlorides, but no change in the amount of calcium.

In 1931, Borst⁴ described a case of duodenal stenosis secondary to a diverticulum and healed ulcer in which the stenosis led to severe vomiting of several days' duration. At autopsy, the patient's kidneys revealed marked degeneration and deposition of calcium in the tubules. In 1932, Porges⁵ presented a similar case in which the same renal changes were observed in a patient with a duodenal ulcer producing stenosis.

In 1933, Cooke⁶ reported 6 cases of pyloric obstruction, in 5 of which the condition was due to an ulcer which was producing stenosis.

3 Zeman, F. D., Friedman, W., and Mann, L. T. Kidney Changes in Pyloric Obstruction, *Proc. New York Path. Soc.* **24**: 41, 1924.

4 Borst, J. G. G. Uramie durch Kochsalzmangel, *Ztschr. f. klin. Med.* **117**: 55, 1931.

5 Porges, O. Ueber Coma hypochloaemicum, *Klin. Wchnschr.* **11**: 186, 1932.

6 Cooke, A. M. Calcification of the Kidneys in Pyloric Stenosis, *Quart. J. Med.* **2**: 539, 1933.

in these 5 cases there were marked degeneration and calcification of the cortical tubules and Henle's loop. In 3 cases there were manifestations of tetany, and in 2 of these ammonium chloride was administered without avail. Cooke explained these renal changes on the basis of the alkalosis which is present in such cases of pyloric obstruction. He did not, however, explain how this alkalosis produces damage to the kidneys. He compared the lesions in these cases with those in cases of death from other causes and was unable to find calcification of the tubules in the latter, except in cases of renal tuberculosis and in 1 case of poisoning by mercury bichloride.

Tschilow,⁷ in 1934 presented a case of duodenal ulcer with stenosis, for which a gastroenterostomy was performed. After the operation the patient continued to have severe vomiting, marked hypochloremia and azotemia developed, and the patient died. At autopsy, the kidneys showed marked calcification of the tubular epithelium.

Gsell,⁸ in 1936, reported 2 cases of pyloric stenosis secondary to ulcers, in 1 of which cases a gastroenterostomy was performed and postoperative ileus occurred. In both cases considerable damage to the kidneys developed, and at autopsy degenerative and calcific changes were observed in the kidneys. Gsell attributed the damage in the kidneys to the hypochloremia and the deposition of calcium to the alkalosis.

In 1936, Rohland⁹ reported 4 cases of vomiting of long duration, in 3 of which the vomiting was secondary to a gastric ulcer which was producing stenosis. In all cases autopsy revealed evidence of "bichloride nephrosis," or calcification of the kidneys, similar to that found in cases of mercury bichloride poisoning. These changes he attributed to both the hypochloremia and the increase in carbon dioxide-combining power. He concluded, therefore, that the "nephrosis" occurring in mercury bichloride poisoning was also due to hypochloremia.

Butler, Wilson and Farber,¹⁰ in 1936, described the case of a boy with obstruction of the upper part of the intestine secondary to mesenteric thrombosis who showed at necropsy multiple deposits of calcium in the tubules of the kidney. They likewise reported 2 cases in which infants with histories of prolonged vomiting (with diarrhea in 1 case) presented no evidence of alkalosis while under observation, but at necropsy showed calcification within the walls of the collecting tubules of the kidneys. The authors cited Lightwood who presented the his-

7 Tschilow, K. Nierenschädigung bei Kochsalzmangel, Wien klin Wchnschr **47** 1324, 1934.

8 Gsell, O. Beiträge zur Hypochlorämie. II. Hypochlorämische Uriämie mit Kalknephrose. Helvet med acta **3** 202, 1936.

9 Rohland, R. Ueber hypochlorämische Nephrose, Klin Wchnschr **15** 826 1936.

10 Butler, A. M., Wilson, J. L. and Farber, S. Dehydration and Acidosis with Calcification of Renal Tubules, J. Pediat **8** 489 1936.

stories of 6 infants with gastroenteritis and vomiting in whom similar deposits of calcium salts within the tubules were observed at autopsy. Results of chemical analyses of the blood of these patients were not given.

In 1937, Pérez-Castio,¹¹ at the Hôst-Wessel Hospital, Berlin, examined the histologic material in 50 cases of pyloric stenosis due to various causes, but essentially secondary to ulcer or carcinoma. In 5 of these cases there were definite and typical renal changes. In a control series of 50 cases no such renal changes were found. In all the 5 cases there were marked hyaline or fatty degeneration of the cells of the tubules, both of the convoluted portion and of Henle's loop, and in 4 of these cases there were also deposits of calcium in these areas. He concluded that the changes in the kidney in these cases of pyloric or high duodenal obstruction with marked vomiting were due to the hypochloremia secondary to the loss of gastric secretion. He noted similar renal changes in the case of mercury bichloride poisoning with hypochloremia. In the fifth case, in which there was hypochloremia and in which the kidneys showed severe degeneration of the renal tubules but no calcification, the patient had received injections of a solution of sodium chloride. Pérez-Castio claimed that the early introduction of sodium chloride therapy in this case prevented deposition of calcium, for the epithelium of the kidney requires a normal content of chloride for its best function. This is significant, as will be seen subsequently. He cited Silio-Vicente, who similarly found that because of the protective action of the chloride ion, injections of sodium chloride were of value in cases of mercury bichloride poisoning. Haden and Orr,¹² and Gamble and Ross,¹³ however, found that the increase of chlorides in the blood by the administration of acid chloride salts, such as ammonium chloride and calcium chloride, did not produce clinical improvement in these patients with pyloric stenosis but in fact made them worse.

Anderson,¹⁴ in 1939, studied 31 cases of renal calcification occurring in infancy and childhood. In 7 of these there were histories of moderate repeated vomiting, which in 2 instances was due to intestinal obstruction. Autopsy revealed particularly severe renal calcification. The main deposits were found within the tubules and chiefly in the convoluted tubules of the cortex.

11 Pérez-Castro, E. Kalknephrose bei Pfortner- oder Duodenalstenose, *Beitr z path Anat u z allg Path* **99** 107, 1937.

12 Haden, R. L., and Orr, T. G. Chemical Changes in the Blood of the Dog After Pyloric Obstruction, *J Exper Med* **37** 365 and 377, 1923.

13 Gamble, J. L., and Ross, S. G. The Factors in the Dehydration Following Pyloric Obstruction, *J Clin Investigation* **1** 403, 1925.

14 Anderson, W. A. D. Renal Calcification in Infancy and Childhood, *J Pediat* **14** 375, 1939.

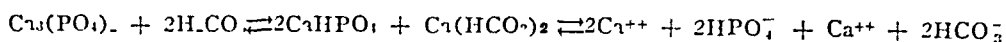
Altogether then, there have previously been reported 46 cases of calcification of the kidney secondary to severe and prolonged vomiting. In most of these cases, the vomiting was due to a cicatricial ulcer of the stomach or the duodenum or to a high intestinal obstruction.

PATHOGENESIS OF CALCIFICATION OF THE KIDNEY

In order to arrive at an adequate explanation for the occurrence of pathologic calcification of the kidney, one has to review briefly the metabolism of calcium in the body and the factors which bring about the solution and precipitation of calcium.

Calcium exists in the normal blood serum in a total concentration of from 9.0 to 11.5 mg per hundred cubic centimeters of blood. This concentration is fairly constant and is little influenced by exogenous factors. The calcium exists in the blood stream in three fractions: (1) calcium in combination with protein, (2) calcium as undissociated but dissolved salts—calcium bicarbonate, $\text{Ca}(\text{HCO}_3)_2$, and tricalcium phosphate, $\text{Ca}_3(\text{PO}_4)_2$, (3) calcium as ionized Ca^{++} ions.

The dissolved calcium salts, as they exist in the presence of sulfate, phosphate and carbonate ions in the blood stream, would immediately be precipitated *in vitro* in the presence of these ions. Likewise, water could keep in solution only 0.0079 per cent of tricalcium phosphate in the presence of alkali carbonates. Yet in the blood stream this salt is present in solution in a concentration of from 0.0110 to 0.0130 per cent, or an amount twice as great as can be held in an aqueous solution *in vitro*. There are two explanations for this unusual solubility. One is the presence of proteins in the blood, which as colloids have the property of keeping otherwise insoluble substances in solution or in suspension (Holt, La Mer and Chown¹⁵). Because of the extremely small proportion of calcium in the plasma (1:10,000) as compared with the concentrations of other substances in the blood, this solution or suspension of calcium is extremely unstable and exists in a delicately balanced condition, aided by the protective action of the plasma colloids. When the total concentration of proteins in the blood diminishes there is a corresponding reduction in the amount of calcium carried in the blood stream. The second physicochemical factor to account for the relatively high concentration of soluble calcium salts is the presence of carbon dioxide, which exists in considerable concentration in the plasma. The relation between the salts of tricalcium phosphate and those of carbonic acid was shown some time ago by Howland¹⁶ in the following formula:



15 Holt, L. E., Jr., La Mer, V. K., and Chown, H. B. Studies in Calcification. I. The Solubility Product of Secondary and Tertiary Calcium Phosphate Under Various Conditions, *J. Biol. Chem.* **64**: 509, 1925.

16 Howland, J. Etiology and Pathogenesis of Rickets in Harvey Lectures, 1922-1923, Baltimore, Williams & Wilkins Company, 1923, vol. 18, p. 189.

O₁, if expressed in another way, "if calcium phosphate is exposed to the action of carbonic acid, an equilibrium is established between dicalcium phosphate and calcium bicarbonate, and between these and calcium ions, HPO₄ ions and HCO₃ ions" Because of the relatively high concentration of carbon dioxide normally present in the blood stream, the calcium phosphate remains dissolved and dissociated, and the equation is "pushed to the right" When, however, the carbon dioxide tension in this solution is reduced, a reversal of this process takes place and tricalcium phosphate is precipitated This reduction of the carbon dioxide tension in a solution containing HCO₃ ions is equivalent to decreasing the hydrogen ion concentration, that is, to making the solution more alkaline

Another factor which may bring about precipitation of calcium is the presence of an excessive concentration of either calcium or phosphorus in the presence of otherwise normal conditions Because of the low solubility of tricalcium phosphate, the serum is normally saturated with this substance Any excess of either ion, therefore, leads to the immediate removal of the other ion, either by excretion or by precipitation If the excess is not removed from the blood stream by excretion, precipitation occurs

Calcium, therefore, is capable of being precipitated by one of several factors, namely, increase of the alkalinity of the blood, reduction in the protein or the carbon dioxide content and changes in the quantity or composition of the calcium salts

After this brief summary of the metabolism of calcium and of its transport in the blood, an attempt may be made to explain the condition of pathologic calcification The calcium present in the kidney in the types of pathologic calcification under consideration exists in two forms, namely, precipitates of tricalcium phosphate and those of calcium bicarbonate The presence of the latter was demonstrated easily by Nazari,¹ who showed that the addition of hydrochloric acid to these calcareous substances dissolved them with the emission of bubbles of carbon dioxide

Now, what is the method of deposition of these calcium salts in the substance of kidney? This condition may occur in the presence of a high concentration of calcium in the blood, such as is seen in diseases of bones, as well as in the presence of a normal concentration of calcium Wells¹⁷ termed the condition occurring with high concentration "metastatic calcification" In this type of calcification there is an oversaturation of the blood with calcium due to the presence of decalcifying lesions of the bones, and the calcium is found to be precipitated in various organs The organs in which this precipitation most frequently

¹⁷ Wells, H. G. *Chemical Pathology*, Philadelphia, W. B. Saunders Company, 1925, p. 486

occurs are the lungs, the stomach and the kidneys. In all these organs there appears to be the common factor of excretion of acids into their cavities. This loss of acid substances leaves the intracellular fluids in the substance of the organ correspondingly alkaline. It is this increased alkalinity of the fluid in the presence of saturation with calcium which causes precipitation of the calcium from the blood stream. The increase in alkalinity makes the calcium salts much less soluble. Under normal conditions the amount of calcium circulating in the blood is too small to be precipitated in this way, but when the blood is saturated with calcium because of absorption from the bones, the increased alkalinity of the blood is apparently sufficient to bring about the deposition of calcium in the tissues mentioned. In the stomach the precipitation occurs between the glands of the parietal cells, or acid-secreting cells. In the lungs, the carbon dioxide is removed from the blood, and precipitation of calcium occurs, for the carbon dioxide is an important factor in keeping these calcium salts in solution in the blood. In the kidney, there is similarly a loss of acid substances in the form of phosphates, sulfates and organic acids, and this leaves the tissue fluids more alkaline. In the presence of the increased alkalinity in these locations, associated with saturation of the blood with calcium, the calcium is precipitated in the substance of these organs, leading to so-called metastatic calcification.

Now, what is the mode of occurrence of calcification of the kidney in the presence of a normal concentration of calcium in the blood, such as appears in these cases of pyloric obstruction? MacCallum¹⁸ has shown experimentally and Ross¹⁹ clinically that the calcium of the blood may exist in normal concentration in cases of pyloric obstruction. In such cases one might attempt to explain the calcification by one of two methods. First, one might explain it by necrosis of the cells of the kidney with subsequent precipitation of calcium salts in these cells. This process, however, is slow and progresses over a long period. Wells, Holmes and Henry²⁰ produced this condition experimentally by prolonged ligation of the renal artery, which subsequently led to injury and to deposition of calcium carbonate in the stroma of the kidney. Here, again, it was the low concentration of carbon dioxide in the necrotic cells and then increased alkalinity which brought about the deposition of calcium in these locations. It is probably by this method that calcification occurs in the old caseous tubercle or in cases of mercury bichloride

18 MacCallum W G, Lintz, J, Vermilve, H N, Leggett, T H, and Boas, E. Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull Johns Hopkins Hosp* **31** 1, 1920

19 Ross, S G. Observations on Tetany, *Canad M A J* **13** 97, 1923

20 Wells, H G, Holmes H F and Henry, G R. Studies on Calcification and Ossification, *J M Research* **25** 373, 1911

poisoning of long standing. In such conditions there is marked destruction of the parenchyma of the kidney with subsequent calcification. This necrosis of kidney cells would not explain calcification in cases of pyloric obstruction, for here the calcification may come on acutely, within forty-eight hours, and though there is microscopic evidence of degeneration of the tubular epithelium of the kidney, the calcification is apparently limited to specific portions of this tubular epithelium.

The explanation for the occurrence of calcification of the kidney is the severe alkalosis present in cases of pyloric or high intestinal obstruction. It has been shown frequently, both clinically and experimentally, that the loss of chlorides in the vomitus in cases of pyloric or high intestinal obstruction brings about an increase in bicarbonate ions of the blood, or alkalosis. It is this increased alkalinity of the blood which leads to the picture of so-called gastric tetany, for in the presence of alkalosis there is a diminution in the amount of available calcium ions, leading to relative hypocalcemia and its accompanying tetany.

But why is the calcification limited to certain areas of the kidney in these cases of excessive alkalosis, and why are other organs not involved? In the presence of alkalosis there is a diminution in respiration and at times periods of complete apnea, in an attempt to elevate the carbon dioxide content of the blood and to overcome the alkalosis (Hartmann and Smyth²¹). There is therefore a diminished exchange of carbon dioxide across the alveolar walls, in an attempt to prevent excessive alkalosis of the tissues. Similarly, in the stomach, in the presence of a prolonged pyloric obstruction, a diminishing amount of hydrochloric acid is secreted into its lumen, in an attempt to maintain the chloride content of the blood. In the kidney, however, the picture appears to be entirely different. In spite of the presence of severe alkalosis caused by a prolonged pyloric obstruction, a strongly acid urine may continue to be secreted. It is on this factor that the calcification of the parenchyma of the kidney depends.

The secretion of an acid urine in these cases of prolonged pyloric obstruction is an attempt to conserve fixed base, such as sodium, of which there is a diminished concentration in the blood (Gamble and Ross,¹³ Hastings, Murray and Murray,²² and Ross¹⁹). Early in these cases of pyloric obstruction there is a compensatory excretion of base in the urine, such as occurs with an "alkaline tide" following the ingestion of a meal. Later, however, there is a deficit in base because of the continued loss of water and alkali in the vomitus. Gamble and Ross

21 Hartmann, A. F., and Smyth, F. S. Chemical Changes in Body Occurring as the Result of Vomiting, *Am J Dis Child* **32** 1 (July) 1926.

22 Hastings, A. B., Murray, C. D. and Murray, H. A., Jr. Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, *J Biol Chem* **46** 223, 1921.

found that sodium was lost in the vomitus to an extent of more than half the equivalent of the chloride loss. They found that after prolonged obstruction the contents of the stomach became decidedly alkaline, instead of acid. The dehydration accompanying the loss of extracellular fluids in these cases of pyloric obstruction, together with the associated starvation, also leads to lowering of the sodium content of the plasma. Likewise, the impaired renal function, due to the extrarenal deviation of the water, as evidenced by the rise in nonprotein nitrogenous products in the blood, leads to impaired production of ammonia by the kidneys. The body, then, has to lose fixed base in an attempt to neutralize the acids of the urine. All of these factors, therefore, lead to a diminution in the total base of the blood in these cases of pyloric obstruction of long duration. This fall in total base may bring its concentration to below 10 per cent of its normal minimum (Gamble and Ross,¹³ Haden and Orr²³). In an attempt to conserve the base for the body in such

TABLE 1—*Secretion of Acid Urine in the Presence of Severe Alkalosis During Experimental Pyloric Obstruction in the Dog (Gamble and Ross¹³)*

12 Hour Specimen, No	Volume, Cc	pH
1	58	6.6
2	46	5.7
3	75	6.3
4*	240	7.9
5	68	7.5
6	70	6.6
7	46	6.4

* Specimen 4 was collected during the period of administration of 1,600 cc. of a 0.9 per cent solution of sodium chloride.

cases, the urine becomes distinctly acid. Maintenance of this acidity of the urine is aided by the increased excretion of organic acids, sulfates and phosphates, which tend to accumulate in the blood in cases of pyloric obstruction.

That this secretion of an acid urine in the presence of severe alkalosis occurs is evident in table 1.

After the administration of sodium chloride, the surplus of sodium over chloride presenting for excretion is conveyed into the urine as bicarbonate, making the urine alkaline. This removal of bicarbonate from the blood causes a fall in the carbon dioxide-combining power, as does the retention of the chloride ion to replace the low chloride content of the blood. The replacement of the low sodium content of the blood and the consequent increase in volume of body fluids help to support the animal and to maintain its weight and vigor. The administration of acid salts such as ammonium chloride and calcium chloride,

23 Haden, R. L., and Orr, T. G. The Sodium Content of the Blood of the Dog After Experimental Intestinal Obstruction, *J. Exper. Med.* **41** 119, 1925.

has been shown by Haden and Orr¹² and by Gamble and Ross¹³ to be harmful rather than beneficial. These substances, by reason of their diuretic action, cause a further loss of sodium which they do not replace, and a further secretion of an acid urine in copious quantity. The animal, therefore, continues to lose body fluids and dies, in spite of the increase in the chloride content of the blood, the decrease in the carbon dioxide-combining power and parenteral administration of fluids.

That such an acid urine occurs clinically in cases of severe alkalosis secondary to pyloric obstruction is evident from an examination of the reported cases in which a record was made of the reaction of the urine. In Brown's² cases 2 and 10 the reaction of the urine was recorded as "acid." Hartmann and Smyth,²¹ in their study of the chemical changes occurring as the result of vomiting, found the urine to be distinctly acid on admission in 4 cases, in spite of the presence of excessive alkalosis of the blood. When the 4 patients were treated with injections of sodium chloride, the urine became alkaline and the patients recovered. In Cooke's⁶ series of cases of renal calcinosis, the reaction of the urine was alkaline in cases 1 and 6 until the patients were given injections of ammonium chloride, after which it became acid. These patients died and at autopsy were found to have extensive calcification. Similarly, Butler, Wilson and Farber¹⁰ found acid urines in the cases of 2 infants with symptoms of prolonged vomiting, in whom autopsy showed extensive calcification of the kidneys. Anderson¹⁴ reported 7 cases in which there were histories of moderately repeated vomiting and autopsy revealed calcification of the kidneys. In 3 of these cases the reaction of the urine was acid. In my own series, an acid reaction was present in the first case, in spite of the presence of severe alkalosis of the blood.

It is this secretion of an acid urine in the presence of severe alkalosis which makes the cell fluids of the kidney even more alkaline and causes a precipitation of calcium salts. Continued secretion of urine is necessary to bring about this precipitation of calcium in the substance of the kidney. That this is true was shown by Wells, Holmes and Henry.²⁰ They found that ligation of the renal artery over a prolonged period led to injury and calcification of the stroma of the kidney. Ligation of the ureter with the production of anemia of the kidney at the same time caused a much smaller amount of calcification. The authors obtained similar results by producing experimental necrosis of renal cells with mercury bichloride. They concluded that this was due to a decreasing secretion of urine by the kidney. Therefore, this further increase in alkalinity of the kidney cells, by reason of the continued secretion of an acid urine, is necessary for the precipitation of calcium in the substance of the kidney.

But why is the renal calcification limited to the convoluted tubules and to Henle's loop, as was found originally by Nazon¹ and frequently substantiated thereafter? The glomeruli are entirely free. Stieglitz²⁴ demonstrated by the use of dyes that when the normal kidney is secreting an acid urine the cells of the parenchymatous tubules, of both the proximal and the distal convoluted tubules and of the loops of Henle, are alkaline in reaction. It is perhaps in these locations that there is either an active secretion of acid substances, such as sulfates and phosphates, into the urine by the tubular cells or a reabsorption of base from the tubular fluid. Richards²⁵ cited Montgomery and Pierce, who found by injecting dyes directly into the distal tubules that the cells which are responsible for the acidification of urine are localized in a region corresponding roughly to the middle third of the distal tubule. It is, therefore, in these locations that there is the greatest increase in alkalinity of the fluids within the tubular epithelium by reason of their sudden loss of acids or gain in alkaline salts. Therefore, the further and marked increase in alkalinity in these locations brings about a precipitation of the calcium from the blood and the production of interstitial calcinosis.

REPORT OF CASES

CASE 1—F. V. R., a 37 year old man, a Puerto Rican, was admitted to the medical service of the Cumberland Hospital on Dec 31, 1937, with a history of gastric distress and occasional vomiting after meals for the past fifteen years. One year before admission he had been at the Mount Sinai Hospital in New York where a series of roentgenograms of the gastrointestinal tract revealed the presence of a benign lesion, probably a cicatrizing ulcer, which was causing stenosis at or near the pylorus. At that time he was placed on a milk and cream diet and was well until six months before admission, when he no longer adhered to his diet. Gastric distress and vomiting returned, for which he took alkalis, with some relief. The vomiting became persistent four days prior to admission. On the day of admission he had spasms of the arms and legs.

Physical examination on admission revealed carpopedal spasm, positive Trousseau and Chvostek signs and marked muscular tenderness with spasm on stimulation of the muscle.

Laboratory examination revealed white blood cells, 22,400, with 71 per cent polymorphonuclears; red blood cells, 3,050,000; carbon dioxide, 108 volumes per cent; calcium, 12 mg per hundred cubic centimeters; phosphorus, 8.1 mg; urea nitrogen, 52.6 mg, and chlorides, 385 mg. The Wassermann reaction of the blood was negative.

The patient was treated for his alkalosis and tetany with intravenous and subcutaneous injections of saline solutions. His acute condition improved, but he continued to vomit copiously, the vomitus being occasionally of coffee ground type. The carbon dioxide-combining power of the blood decreased to 88 volumes per cent, the blood chlorides rose to 440 mg per hundred cubic centimeters, and

24 Stieglitz, E. J. Histologic Hydrogen-Ion Studies of the Kidney. *Arch Int Med* 33: 483 (April) 1924.

25 Richards, A. N. Physiology of the Kidney. *Bull New York Acad Med* 14: 5, 1938.

he appeared relatively comfortable. However, during the time of treatment the amount of urea nitrogen ranged between 41 and 72 mg per hundred cubic centimeters, and a renal function test showed fixation of specific gravity at 1.010, with compensatory polyuria. A series of roentgenograms of the gastrointestinal tract revealed the presence of a pyloric obstruction, with "soup bowl" stomach. Operative intervention seemed to be the only treatment for his condition. He was therefore prepared with transfusions and parenteral administration of fluids for a period of two weeks, and was then transferred to the surgical service.

The operation was performed on January 17, after a transfusion of 500 cc of citrated blood. Gastric resection with duodenal exclusion and a Polya gastrojejunostomy were performed.

Immediately after the operation the patient's condition was good. Continuous Wangensteen suction was instituted after he showed response, and remained in place for forty-eight hours, draining some bile and intestinal secretion but no blood. Fluids were forced parenterally. On the third day the patient began to

TABLE 2—*Laboratory Data in a Case of Gastric Tetany and Alkalosis Associated with Pyloric Obstruction and Renal Calcinosi*s

Date	Calcium, Mg per 100 Cc	Phosphorus, Mg per 100 Cc	Carbon Dioxide, Vol %	Urea Nitrogen, Mg per 100 Cc	Chlorides, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Albumin, Mg per 100 Cc	Globulin, Mg per 100 Cc	Icteric Index
12/31/37	12.0	8.1	108						
1/ 2/38			88.68	52.6	385	4.0			
1/ 4/38				60.0		5.0	6.3	3.1	
1/ 6/38			60	41.0		3.6			
1/ 7/38					440				12.3
1/ 9/38			93						(van den Bergh's test positive)
1/10/38	10.0	13.7	88	72.9	364				Indirect
1/11/38			20		244				
1/12/38			52	42.2	175				
1/13/38			79	43.2	370				
1/14/38			90		450				
1/20/38			40	14.0					
1/21/38			41						

The specimens of urine on January 4, 11, 20 and 21 were acid.

complain of epigastric pains but did not have nausea or vomiting. His abdomen was distended, and a low enema of soapsuds and oil was ineffectual. The distention yielded, however, to Wangensteen suction and the Harris drip. The operative wound was clean and showed no evidence of evisceration. The temperature at this time was 103 F, with the pulse rate in proportion. The following (fourth postoperative) day the temperature fell slightly, but the pulse rose to between 120 and 140 a minute and was weak. He appeared dehydrated and anxious and complained of thirst despite a seemingly adequate intake of fluid, of 3,500 to 4,000 cc per day. Respirations were rapid. His abdomen became distended and was tender throughout, though more so in the right lower quadrant. Laboratory examination revealed 99 mg of sugar and 14 mg of urea nitrogen per hundred cubic centimeters of blood and a carbon dioxide-combining power of 41 volumes per cent. He was given a transfusion of 250 cc of citrated blood, but his pulse rate remained elevated at 140 a minute, and the quality was weak. His abdomen remained distended. He died on the fifth day after operation.

Autopsy.—Postmortem examination revealed generalized purulent peritonitis secondary to leakage of intestinal contents through the sutured duodenal stump, which contained an acute necrotic ulcer. Both kidneys showed an extensive peri-

tubular deposition of calcium in the vicinity of the convoluted as well as of the collecting tubules, a deposit which in some areas reached large proportions. The calcium was located immediately beneath the tubular epithelium, between the tunica propria and the epithelial cells of the tubules, and not in the capillaries. The rest of the kidneys showed cloudy swelling. The glomeruli were intact, there was no inflammatory infiltrate and no abnormality in the blood vessels.

Comment—In this case were shown the classic signs of gastric tetany in the presence of alkalosis due to prolonged vomiting and secondary to a pyloric obstruction. Throughout most of the preoperative period, the patient's carbon dioxide-combining power was distinctly above normal, and the urea nitrogen was markedly and constantly elevated in spite of an apparently sufficient preoperative intake of fluid. This intake seemed inadequate, however, for in spite of the apparent alkalosis the patient secreted an acid urine and had a low content of chlorides and a retention of nitrogen in the blood. It was this acid urine in the presence of alkalosis that accounted for the universal renal calcinosis and its associated poor renal function.

CASE 2—P. G., a 49 year old white man, was admitted to the hospital on Jan. 17, 1938, with a history of epigastric and substernal pains for one and a half years, and of a loss in weight of 22 pounds (10 Kg.) during this period, chiefly from dietary restrictions. These pains had increased during the week previous to admission. He had vomited persistently during the previous two days.

Physical examination on admission revealed that the patient was chronically ill, with moderate distention of the upper part of the abdomen. The edge of the liver was palpable just below the costal margin, but was not nodular. Reducible inguinal hernia was present bilaterally. A series of gastrointestinal roentgenograms revealed a juxtapyloric duodenal ulcer with partial obstruction. Analysis of the gastric contents revealed a normal quantity of hydrochloric acid and the presence of blood. The stools gave a positive reaction for occult blood. The Wassermann reaction of the blood was negative.

The patient was treated conservatively for three and a half weeks and secured only partial relief with alkalis and the Sippy diet.

Operation on February 9 revealed a "pre- and postpyloric mass involving the stomach, pancreas and adjacent lymph glands." Soft glands were palpated in the gastrohepatic and the gastrocolic omentum. A posterior gastroenterostomy was performed.

The patient's condition immediately after the operation was good. About five hours later he complained of a severe, sharp pain in the abdomen, radiating from the right flank medially to the right upper quadrant and the epigastrium. He became anxious and worried. His abdomen was moderately firm and tender, with no specific points of maximal tenderness.

On the first day after operation his temperature rose to 104 F., and his pulse rate was 120 a minute. The respiratory rate was 30 a minute and breathing was deep and laborious. No abnormal signs were found in his chest. His abdomen was moderately firm, but not especially tender. Examination of his chest with a portable roentgenographic apparatus showed nothing abnormal. The following day his condition remained unchanged. His temperature was 103.2 F. His abdomen was moderately distended and was tender in the right lower quadrant. On the third postoperative day his temperature was 102 F. Chemical examination of the blood

revealed urea nitrogen, 34 mg, sugar, 156.2 mg, and chlorides 625.0 mg, per hundred cubic centimeters. On the fourth postoperative day he was toxic and drowsy. The lower part of his abdomen was distended and tympanic. He was given a transfusion of blood, fluids by parenteral injection, sedatives and a Harris drip. Chemical analysis of the blood at this time revealed the carbon dioxide-combining power of the blood to be 38 volumes per cent and the creatine content 1.5 mg per hundred cubic centimeters.

On the fifth postoperative day examination of his chest showed impairment of percussion note in the right axilla and in the bases of both lungs, with numerous adventitious sounds. There was increased distention of the lower portion of the abdomen. On medical consultation, evidences of consolidation of the bases of both lungs were found, and use of the oxygen tent was advised. On the sixth day roentgenograms of the chest revealed evidence of infiltration at the bases of both lungs. He became increasingly cyanotic, psychotic and restless and died on the seventh postoperative day.

Autopsy—Postmortem examination revealed generalized purulent peritonitis secondary to a perforating chronic duodenal ulcer. There was no evidence of any leakage through the gastro-enterostomy stoma. There was bilateral hypostatic

TABLE 3—*Laboratory Data in a Second Case of Renal Calcification Accompanying Pyloric Obstruction**

Date	Urea Nitrogen, Mg per 100 Cc	Creatine, Mg per 100 Cc	Sugar, Mg per 100 Cc	Chlorides, Mg per 100 Cc	Carbon Dioxide Vol per Cent
2/12/38	34.0		156.2	625	
2/13/38		1.5			38
2/14/38	16.3	1.1		650	42

* The urine on January 18 was alkaline, with triple phosphate crystals, on January 20 alkaline and on January 31 neutral.

pneumonia. Both kidneys showed extensive peritubular deposits of calcium within the parenchyma of the cortex. In some areas the calcium had broken through the tubules into the lumen.

Comment—In this case, although there was a history of persistent vomiting of several days' duration prior to operation, determination of the chemical constituents of the blood was not made during this period. Postoperatively the patient showed some retention of urea nitrogen in the blood, probably secondary to the extensive renal calcinosis found at autopsy. In this case there may have been the same changes in the blood as were present in the first case, but no proof could be had, for preoperative chemical determinations were not performed. The renal damage, however, was of the same character and almost of the same magnitude as that in the first case.

CASE 3—W. C., a 68 year old white man, was admitted to the Cumberland Hospital on Feb. 10, 1938, with the history of persistent vomiting, cramplike abdominal pains and obstipation of ten days' duration.

Physical examination on admission revealed that the patient appeared chronically ill and anemic and showed evidences of severe loss of weight. Examination of his abdomen showed it to be moderately distended, soft and tympanic through-

out, with peristalsis visible through the abdominal wall. His temperature was 101 F. The urine was acid in reaction and showed a faint trace of albumin. The blood count revealed a hemoglobin content of 65 per cent, red blood cells 4,560,000 and white blood cells 12,600, with 87 per cent polymorphonuclears. A flat roentgenogram of the abdomen revealed the presence of fluid levels and marked distention of the coils of the colon and small intestine.

The patient was treated conservatively for twelve hours with gastric lavage and clysis, with no evident improvement.

On the day after admission, operation with the area under local anesthesia revealed marked distention of the loops of the small intestine and a malignant growth in the midjejunum, which was the cause of the obstruction. A side to side anastomosis was performed, and the patient was given a transfusion. His condition immediately after the operation was good. He passed gas and fecal contents through the anus. Two days later, however, his abdomen became distended and his general condition poor. Subsequently, on the fifth postoperative day, there developed painful parotitis on the left side and signs of pneumonia

TABLE 4—*Laboratory Data in a Third Case of Renal Calcification Accompanying High Intestinal Obstruction**

Date	Sugar, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Chlorides, Mg per 100 Cc	Cholesterol Mg per 100 Cc
2/11/38	159.4	36.4	640	145.3
2/15/38		14.2	640	

* The urine on February 10 was acid, with a faint trace of albumin, and on February 16, alkaline, with a negative reaction for albumin.

in the right lung. On the twelfth postoperative day, his abdomen became markedly distended and tender, and enemas were ineffectual. The patient became cold and cyanotic, his pulse became imperceptible, and he died.

Autopsy—Postmortem examination revealed a carcinoma of the jejunum and the jejunojejunostomy stoma, with an intussusception of the distal loop of the jejunum into the proximal loop, carrying with it the growth and enterostomy stoma. There was generalized peritonitis, secondary to a perforation found in the jejunum, cultures from which revealed *Bacillus welchii*, *Bacillus coli* and a nonhemolytic streptococcus. There was evidence of renal calcinosis in both kidneys, extratubular in distribution. There were several atrophic tubules and hyalinized glomeruli with areas of lymphocytic infiltrate in the cortex. There was some thickening of the arterioles.

Comment—In this case, too, the patient had persistent vomiting of ten days' duration but determination was not made of the carbon dioxide-combining power of the blood. The urine, however, was acid in reaction on admission, and there was evidence of retention of urea nitrogen. Subsequently secondary intestinal obstruction developed, due to the postoperative intussusception of the enterostomy stoma, and the patient continued to vomit. Autopsy showed fairly extensive peritubular calcification in both kidneys.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

RUSSELL M WILDER, M D, P H D

HARRY C BROWNE, M D

Fellow in Medicine, the Mayo Foundation

AND

HUGH R BUTT, M D

ROCHESTER, MINN

I DISEASES OF METABOLISM

By DR WILDER AND DR BROWNE

DIABETES MELLITUS

Genesis—(a) Pituitary Gland and Carbohydrate Metabolism In last year's review ¹ attention was directed to the significance of Young's production of permanent diabetes in dogs by repeated injections of crude extracts of anterior lobes of beef pituitaries for a long period. This work, together with the more significant literature that bears on the relation of the anterior lobe of the pituitary to carbohydrate metabolism, is reviewed by Young ² in a readable paper which he gave before the section of physiology at the annual meeting (1939) of the British Medical Association. A tentative general conclusion from experiments of Long, Russell, Bennett ³ and others assigns to the secretion of the anterior lobe of the pituitary a depressive action on the oxidation of carbohydrate in the muscles and promotion of glycogen storage. Since the storage of glycogen can be promoted also by crystalline adreno-

From the Division of Medicine, the Mayo Clinic

1 Wilder, R M, Rutledge, D I, and Wilbur, D L Diseases of Metabolism and Nutrition, Review of Certain Recent Contributions, Arch Int Med **63** 356-427 (Feb) 1939

2 Young, F G The Relation of the Anterior Pituitary Gland to Carbohydrate Metabolism, Brit M J **2** 393-396 (Aug 19) 1939

3 Long, Russell and Bennett, cited by Young ² Long, C N H Influence of Pituitary and Adrenal Glands upon Pancreatic Diabetes, Medicine **16** 215-247 (Sept) 1937 Russell, J A, and Bennett, L L Maintenance of Carbohydrate Levels in Fasted Hypophysectomized Rats Treated with Anterior Pituitary Extracts, Proc Soc Exper Biol & Med **34** 406-409 (May) 1936

cortical substances,⁴ the suggestion is made that this pituitary effect is mediated by stimulation of the adrenal cortex. Corey⁵ reported that administration of corticoadrenal extract to fasting hypophysectomized rats will restore to normal the values for blood sugar and those for liver and muscle glycogen. This also attests to the operation of the hypophysis through the adrenal cortex in its effect on carbohydrate metabolism. However, Fry, Long and Ritter,⁶ with adrenalectomized, depancreatized rats in which glycosuria was maintained at a constant level by daily oral administration of adrenocortical extract, found that injection of anterior pituitary extract increased the glycosuria. This they interpreted to indicate that the anterior portion of the pituitary influences carbohydrate metabolism not only through the action of an adrenotropic factor but also through an effect exerted by another factor (or factors) acting directly on the tissues.

The claim of Anselmino, Herold and Hoffman⁷ that the administration of a certain fraction of anterior pituitary extract to normal rats resulted in a few days in a substantial increase in the number and size of the islands of Langerhans and that this established the presence of a pancreatropic hormone among the secretions of the pituitary is not acceptable. With Richardson, Young² had confirmed the observation that crude pituitary extracts injected into rats increased the amount of island tissue in the pancreas, and later, with Marks, Young² showed that the amount of insulin in the pancreas of the rat so treated was greatly increased. The rat, unlike the dog, could not be made diabetic by injections of pituitary extracts, and the explanation of the hypertrophy of the islands seems to lie in the capacity of the island tissue of this species to hypertrophy rapidly and to increase its function in response to the increased demand for insulin created by the injections of pituitary extracts. Even in dogs the response to long-continued treatment with pituitary extracts is irregular. Some dogs cannot be made diabetic by this means, as has been noted not only by Young² but by those who have repeated his experiments.

The ketogenic activity of the anterior lobe of the pituitary has received much attention since Burn and Ling⁸ fed cats fat and observed

4 Long, C. N. H., and Katzin, B. Effect of Adrenal Cortical Hormone on Carbohydrate Stores of Fasted Hypophysectomized Rats, *Proc. Soc. Exper. Biol. & Med.* **38** 516-518 (May) 1938.

5 Corey, E. L. Hypophyso-Adrenal Synergy and Carbohydrate Metabolism, *Am. J. Physiol.* **126** 470 (July) 1939.

6 Fry, E. G., Long, C. N. H., and Ritter, H. B. The Aggravation of Pancreatic Diabetes by Adrenal Cortical Extract, *Am. J. Physiol.* **126** 497 (July) 1939.

7 Anselmino, K. J., Herold, L., and Hoffman, F. Ueber die pankreatrope Wirkung von Hypophysenvorderlappeneextrakten, *Klin. Wchnschr.* **12** 1245-1247 (Aug. 12) 1933, cited by Young.

excretion of ketone bodies when anterior pituitary extract was injected. The ketosis, as was shown by Best and Campbell,⁹ may be accompanied by the development of a fatty liver at the expense apparently of the fat depots of the body. It also was established satisfactorily that the ketosis of depancreatized dogs could be diminished by hypophysectomy, and thus it appeared that the secretions of the anterior lobe of the pituitary play a part in the production of ketosis. How this is accomplished remains uncertain, but from what follows it seems unlikely that a special pituitary hormone, a regulator of fat metabolism, is involved. Anselmino and Hoffman¹⁰ had claimed success in separating a "fat metabolism hormone" from pituitary extracts, but in Young's opinion ketosis can be explained more simply by the general effects on metabolism of secretions of the anterior lobe of the pituitary, namely, the decreased oxidation of carbohydrate and the decreased catabolism of protein. These effects throw the burden of supporting necessary heat production on fat stores, and at the same time, by the thyrotropic effect of the pituitary extracts, the rate of heat production is increased. This view is held also by Shipley and Long¹¹ who were unable to confirm the work of Anselmino and Hoffman. Comparative assays of the various fractions of anterior pituitary extracts indicated that ketogenic activity accompanied the fractions containing growth and diabetogenic hormones. They commented on their results as follows:

The practice of assuming that the multiple effects of anterior pituitary extracts upon metabolism are due to separate hormones does not seem desirable in the absence of any chemical evidence that this is the case. On the contrary, a consideration of the known facts of metabolism indicates that some of the alterations produced by the injection of anterior pituitary extracts may be regarded as secondary consequences of their action. Among these we suggest the production of ketosis may be included.

A graphic presentation of the interplay of the endocrine glands in carbohydrate metabolism was contributed by Roger¹² (figure). G. H.

8 Burn, J. H., and Ling, H. W. Ketonuria in Rats on a Fat Diet. (a) After Injections of Pituitary (Anterior Lobe) Extract, (b) During Pregnancy, *J. Physiol.* **69** ix, 1930.

9 Best, C. H., and Campbell, J. Effect of Anterior Pituitary Extracts on Liver Fat of Various Animals, *J. Physiol.* **92** 91-110 (Feb. 16) 1938.

10 Anselmino, K. J., and Hoffman, F. Das Fettstoffwechselhormon des Hypophysenvorderlappens. I. Nachweis, Darstellung und Eigenschaften des Hormons, *Klin. Wchnschr.* **10** 2380-2386 (Dec.) 1931, Zur Darstellung des Fettstoffwechselhormons des Hypophysenvorderlappens, *Endokrinologie* **17** 1-8, 1936.

11 Shipley, R. A., and Long, C. N. H. Studies on the Ketogenic Activity of the Anterior Pituitary. III. The Nature of the Ketogenic Principle, *Biochem. J.* **32** 2249-2256 (Dec.) 1938.

12 Roger, H. Quelques travaux recents sur la physiologie du foie, *Presse med.* **47** 1104-1106 (July 12) 1939.

Roger and Léon Binet are the editors of "Traite de physiologie normale et pathologique" The third volume of this large work covers the physiology of the liver and kidneys, and recently has appeared in a second edition. Reviewing the many new acquisitions in knowledge of the liver since the appearance of the first edition of volume 3 in 1928, Roger names nineteen hormones with activities affecting the glycogenic function of the liver. The first fifteen of these, listed below, he regards as "bien connues." The bracketed material is ours.

A Hormones elaborated by the anterior lobe of the pituitary

- 1 Diabetogenic hormone (Houssay)
- 2 Hypophysopancreatic hormone, a stimulant of the islands of Langerhans [This is not generally accepted. The effect noted can be explained by the capacity of the islands to hypertrophy in response to the increased demand for insulin created when anterior pituitary extracts are administered.]
- 3 Hypophysothyroid hormone (Collip)
- 4 Hypophysoparathyroid hormone with action on the pancreas by relay through the parathyroid glands [The evidence for this is not impressive.]
- 5 Hypophysomedulloadrenal hormone [Questionable.]
- 6 Hypophysocorticoadrenal hormone (Collip)
- 7 Contrainsular hormone (Lucke) [See earlier review¹³. Evidence accumulated since that review was written throws considerable doubt on the existence of this hormone.]

B Intermediary hormones

- 8 Corticomedullary hormone [This factor probably occurs, but the evidence is inconclusive.]
- 9 Thyropancreatic hormone [Not established, the effects noted can be explained by the demand for more insulin created by the elevation of the rate of metabolism¹⁴.]
- 10 Thyroadrenal hormone [Not established, the effects noted can be explained by the elevation of the rate of metabolism.]
- 11 Parathyropancreatic hormone [See comment under heading A4.]
- 12 Duodenopancreatic hormone (Incretine of LaBarie) [See comments on this in an earlier review¹⁵.]

C Hepatotropic hormones

One of these, the pituitary diabetogenic hormone (Houssay), is already named. [See heading A1.]

- 13 Pancreaticohepatotropic hormone (insulin)
- 14 Medulloadrenohepatotropic hormone (epinephrine)
- 15 Corticoadrenohepatotropic hormone (corticosterone)

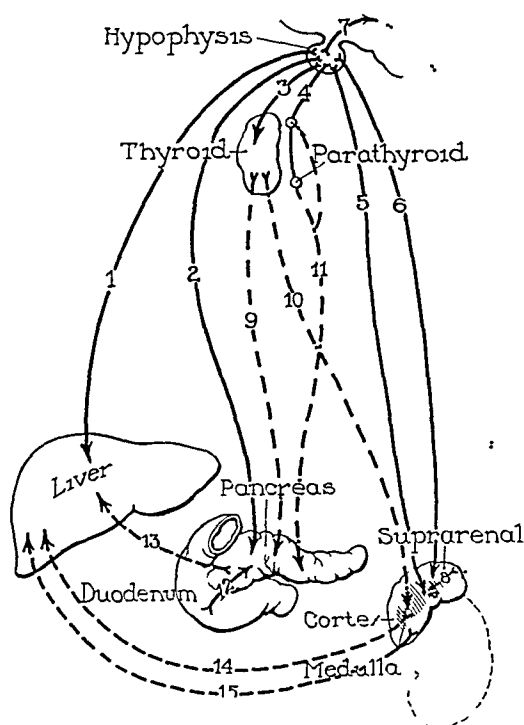
13 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **55**: 304-343 (Feb.) 1935.

14 Wilder, R. M. Hyperthyroidism, Myxedema and Diabetes, *Arch. Int. Med.* **38**: 736-760 (Dec.) 1926.

15 Wilder, R. M. and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **57**: 422-471 (Feb.) 1936.

The following comments in this article by Roger¹² should arouse the interest of American readers

The glycogen of the liver has long been regarded as a reserve for furnishing the organ with the sugar which it constantly requires. This, indeed, is an important role, but recent studies lead to the conclusion that almost all, not to say all, of the chemical activities of the liver depend on the integrity of its glycogen function. Glycogen enables, or at least facilitates, the utilization of certain hexose sugars, notably galactose. It gives birth to citric acid. It enables conjugation with a great number of toxic substances to form inoffensive glucuronates which can readily be excreted by the kidneys. Glycogen furnishes the dextrose for the intrahepatic formation of neutral fats from the soaps carried to the liver from the intestine. [This statement, we suppose, may offend the ears of American physi-



Interplay of endocrine glands in carbohydrate metabolism. See text, page 393, for significance of numbers 1, 2, 3, 4 and so forth. (From Roger¹²)

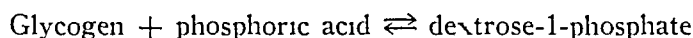
ologists. See Best and Taylor¹⁶] Glycogen intervenes in the transformation of fatty acids, which under its influence are progressively desaturated and in consequence more readily oxidized. The normal devolution of the lipoids results in the formation of the intermediate ketone bodies. They, being injurious, must rapidly be eliminated or destroyed, and much research has established that the values for the ketones rise as those for hepatic glycogen fall, and vice versa. The transformation of nitrogenous metabolites likewise is subordinate to the glycogen of the liver, which must be intact to permit the formation and transformation of aminoacids, creatine and urea. Furthermore, glycogen serves to maintain the hepatic parenchyma and to make possible its regeneration. Glycogen

16 Best, C H, and Taylor, N B. *The Physiological Basis of Medical Practice*, ed 2, Baltimore, Williams & Wilkins Company, 1939, p 949

intervenes in the arrest and destruction of microbes, as well as in many other hepatic functions of minor importance. Thus have modern studies amplified unexpectedly the great discovery of Claude Bernard.

(b) Artificial Synthesis of Glycogen. Adding even more unexpectedly to the great discovery of Claude Bernard is the accomplishment this year of an *in vitro* synthesis of glycogen by Cori, Schmidt and Cori¹⁷ and Cori, and Schmidt¹⁸. Besides representing the first successful synthesis of any high molecular polysaccharide, the work leading to this discovery explains much of the enzymatic process which normally is involved in the polymerization of dextrose to glycogen and the degradation of glycogen—to sugar in the liver and to lactic acid in the muscle.

Solutions of purified enzyme prepared from muscle, heart, brain, liver and yeast were shown to catalyze the following reaction in a reversible manner:



When andenylic acid (which acts as a coenzyme) is added to a solution of dextrose-1-phosphate containing the enzyme obtained from the liver (liver-phosphorylase), inorganic phosphate is liberated and a polysaccharide is formed which gives a brown color with iodine and which in other chemical properties is indistinguishable from glycogen. At the point of equilibrium of the reaction, glycogen + phosphoric acid \rightleftharpoons dextrose-1-phosphate, the ratio of concentration of inorganic phosphate, which represents glycogen formed to concentration of dextrose-1-phosphate, at 30 C is 83.5 to 16.5, or 5.1 to 1.

(c) Adrenal Glands and Carbohydrate Metabolism. Interest continues to center on the importance in carbohydrate metabolism of the adrenal cortex. In last year's review¹ mention was made of the observation of Long, Fry and Thompson that crystalline compounds isolated from the adrenal cortex by Kendall provoked glycosuria in partially depancreatized rats. Now synthetic adrenocortical material has been made available by Steiger and Reichstein¹⁹. Although highly potent so far as activity in salt water metabolism is concerned, the synthetic material, we are informed, lacks the power to provoke diabetes in partially depancreatized rats. Also we ourselves observed that a daily dose of 30 mg. of it injected subcutaneously did not appreciably raise

17 Cori, C. F., Schmidt, G., and Cori, G. T. The Synthesis of a Polysaccharide from Glucose-1-Phosphate in Muscle Extract, *Science* **89** 464-465 (May 19) 1939.

18 Cori, C. F., Cori, G. T., and Schmidt, G. The rôle of Glucose-1-Phosphate in the Formation of Blood Sugar and Synthesis of Glycogen in the Liver, *J. Biol. Chem.* **129** 629-639 (Aug.) 1939.

19 Steiger, M., and Reichstein, T. Desoxy-cortico-steron (21-oxy-progesteron) aus Δ^5 -3-oxy-atio-cholensaure, *Helvet. chim. acta* **20** 1164-1179, 1937.

the level of the blood sugar or increase the twenty-four hour excretion of dextrose in a case of diabetes. The data of this experiment are given in table 1.

That absence of adrenocortical activity frequently is associated with an abnormally low level of blood sugar has long been known from observation of patients with Addison's disease. According to Feriebee, Ragan, Atchley and Loeb,²⁰ the synthetic compound, desoxycorticosterone acetate, has no influence on this abnormality, an observation that we can confirm from personal experience in 14 cases of Addison's disease in which desoxycorticosterone acetate was used therapeutically. Thus it seems probable that the synthetic preparation, while possessing many of the properties of active extracts of adrenal cortex, may be

TABLE 1—*Absence of Effect of Desoxycorticosterone Acetate on the Glycosuria of Diabetes Mellitus**

Date, 1939	Period, Days	Daily Dose		Daily Average Grams in Urine		
		Desoxycorticosterone Acetate, Mg	Insulin, Units	Sugar	Nitrogen	Sodium
July 7-16	10	0	60	30.8		
July 17-23	7	30	60	33.4	9.93	2.75
July 24-30	7	0	60	32.8	10.57	4.69
July 31-Aug 7	8	30	60	26.9	9.67	2.28

* The patient, a woman 19 years of age, had diabetes of eight years' duration. Rest in bed was maintained, and a constant diet was given. It provided 140 Gm of carbohydrate, 78 Gm of protein, 90 Gm of fat and 9 Gm of sodium chloride. Soluble insulin was injected twice daily. The dose was previously adjusted so as to permit a moderate degree of glycosuria.

The absence of effect of desoxycorticosterone on this glycosuria is the more striking in view of the definite retention of sodium ion encountered in the periods when desoxycorticosterone acetate was administered. The intake of sodium ion was reasonably constant, varying only with the sodium content of the food before seasoning.

It is worthy of comment that a daily dose of 30 mg of desoxycorticosterone acetate is from three to six times as large as the dose necessary to correct the disturbances of salt and water metabolism in patients with severe adrenocortical insufficiency.

qualitatively dissimilar from the adrenocortical hormone, at least in some respects.

An abnormality of Addison's disease related to the frequent occurrence of hypoglycemia is hypersensitivity to insulin. Swann and Fitzgerald²¹ investigated the relative importance of the adrenal medulla and the adrenal cortex in the maintenance of normal sensitivity to insulin. They found that in rats from which both adrenal glands had been removed sensitivity was twenty-four times as great as in controls but that the major part of this abnormality could be abolished by transplanting the removed cortical tissue to the ovary.

20 Feriebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F. Desoxycorticosterone: Certain Effects in the Treatment of Addison's Disease, *J. A. M. A.* **113**: 1725-1731 (Nov. 4) 1939.

21 Swann, H. J., and Fitzgerald, J. W. Insulin Shock in Relation to Components of Adrenals and Hypophysis, *Endocrinology* **22**: 687-692 (June) 1938.

The respiratory quotient of the depancreatized dog is low and, unlike the corresponding quotient of the normal animal, it remains low after the animal is fed carbohydrate. Chambers, Sweet, Chandler and Lichtman²² studied this quotient in dogs after adrenalectomy with pancreatectomy (the Young preparation) and after hypophysectomy with depancreatectomy (the Houssay operation). The failure of the respiratory quotient to rise after carbohydrate is fed, although still a matter of contention, is generally accepted as an index of deficient oxidation of carbohydrate. The abnormality, as was stated, is regularly observed in depancreatized but otherwise unchanged dogs. It also is characteristic of severe clinical diabetes. The respiratory quotients of the adrenalectomized and depancreatized dogs were not elevated significantly by carbohydrate. The basal respiratory quotients of these animals were low, and when dextrose was given the quotients of only a few of them rose. Essentially the same results were obtained with dogs subjected to the Houssay operation. Thus it cannot be said, as some have supposed, that adrenalectomy or hypophysectomy abolishes preexistent diabetes.

(d) *Pancreas and Fat Metabolism*. In an earlier review Wilbur and I²³ commented on the development of fatty liver in depancreatized dogs sustained with insulin. This, as was said, could be prevented if the animals were given, with their food, raw pancreas, lecithin, choline, betaine or an extract made from the pancreas by Diagstedt and called by him lipocarc. To judge from an observation by Hansen²⁴ and a more recent study by White, Marble, Bogan and Smith,²⁵ the large fatty livers of poorly treated diabetic children are imperfectly related to the condition found in depancreatized dogs. White and her associates gave raw pancreas to 2 diabetic children with hepatomegaly and betaine to 12 other children with a similar disease. No significant change in the size of the liver in any of these children was observed after the feeding of pancreas, and a minor change only in the livers of 6 of the children receiving betaine. On the other hand, hepatomegaly was corrected in 15 (nearly 80 per cent) of 19 little patients who received nothing but protamine insulin, which controlled the diabetes. In our experience there has not been a single case in which the type of hepato-

22 Chambers, W. H., Sweet, J. E., Chandler, J. P., and Lichtman, A. L. Carbohydrate Metabolism in Adrenalectomized, Depancreatized Dogs, *Am. J. Physiol.* **126** 460-461 (July) 1939.

23 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition, Review of Certain Recent Contributions, *Arch. Int. Med.* **59** 329-364 (Feb.) 1937.

24 Hansen, P., cited by Wilder and Wilbur²³.

25 White, P., Marble, A., Bogan, I., and Smith, R. M. Enlargement of the Liver in Diabetic Children. II. Effect of Raw Pancreas, Betaine Hydrochloride and Protamine Insulin, *Arch. Int. Med.* **62** 751-764 (Nov.) 1938.

megaly described by White and her associates failed to respond to satisfactory control of the diabetes. This clinical experience provides little reason to believe that deficiency of lipocaic or of other secretion of the pancreas involved in fat metabolism is a practical problem in diabetes except, perhaps, in those rare cases in which the pancreas as a whole is destroyed by gross diabetic disease. However, Dragstedt and his associates²⁶ now emphasize that two types of fatty infiltration are encountered in experimental pancreatic diabetes and possibly also in clinical diabetes. One type is due to a failure to control diabetes, as when the administration of insulin has been inadequate. This type is characterized by a normal or a high concentration of lipoids in the blood and by acidosis. The second type is due to insufficiency of lipocaic. It is associated with a low concentration of blood lipoids, impaired hepatic function, increased sensitivity to insulin and decreasing requirements for insulin. The first type is relieved by insulin, but not the second. That fatty infiltration and enlargement of the liver of the second type also occur in human diabetes is suggested in 3 cases reported by Grayzel and Radwin²⁷ and a fourth reported by Rosenberg²⁸. The patients of Grayzell and Radwin²⁷ were young diabetic subjects with hepatomegaly. Their diabetes was well controlled with diet and insulin. The large livers diminished in size when lipocaic was administered, increased in size when lipocaic was withheld and again diminished in size when treatment with lipocaic was resumed. Rosenberg's patient was an adult with mild diabetes. Hepatomegaly was marked and was associated with impairment of liver function. These conditions were not improved by better control of the diabetes but did respond to treatment with lipocaic. Specimens of liver secured at operations before and after treatment with lipocaic also revealed disappearance of fat.

In this connection certain recent observations bearing on the role of the alpha cells of the islands of Langerhans are of great interest. They were made by disciples of that grand old student of the pancreas who for forty years has headed the department of anatomy at the University of Chicago, Robert Bensley. Woerner,²⁹ in the last of a

26 Dragstedt, L. R., Vermeulen, C., Goodpasture, W. C., Donovan, P. B., and Geer, W. A. Lipocaic and Fatty Infiltration of the Liver in Pancreatic Diabetes, *Arch Int Med* **64** 1017-1038 (Nov.) 1939.

27 Grayzel, H. G., and Radwin, L. S. Hepatomegaly in Juvenile Diabetes Mellitus Treated with Pancreatic Extract, *Am J Dis Child* **56** 22-32 (July) 1938.

28 Rosenberg, D. H. Proved Case of Recovery from Fatty Metamorphosis of the Liver After Treatment with Lipocaic, *Am J Digest Dis* **5** 607-613 (Nov.) 1938.

29 Woerner, C. A. The Effects of Continuous Intravenous Injection of Dextrose in Increasing Amounts on the Blood Sugar Level, Pancreatic Islands and Liver of Guinea Pigs, *Anat Rec* **75** 91-105 (Sept.) 1939.

series of papers to come to our attention, has this to say regarding the results of repeated injections of solutions of dextrose into guinea pigs. The injections were made at rates of from 1 to 3 Gm per kilogram of body weight per hour over periods of days.

The results indicate that when the intravenous injection of dextrose is accompanied by considerable hyperplasia and secretory activity of the beta cells and the blood sugar level is raised only slightly above the feeding level, the alpha cells may be exhausted and even hydropic, little glycogen may be stored in the liver and no osmic combining fat is found there.

When the injection is accompanied by actively secreting and exhausted beta cells with some mitotic activity and the blood sugar level is considerably raised (i.e., two to three times the normal level in 24 to 48 hours), the alpha cells may be actively secreting and somewhat suppressed, the liver cells may be filled with glycogen and very little osmic combining fat found in that organ.

This statement, as we interpret it, represents the response of a still efficient pancreas. On the other hand, when a sufficient degree of exhaustion and degeneration of the insulin-producing cells of the pancreas was produced, as seems to have occurred in some of these animals, the following was noted:

When the blood sugar level is excessively high, the beta cells exhausted and degenerating or suppressed, the alpha cells may be almost completely suppressed, the liver cells distended with glycogen and increasing amounts of osmic combining fat found in the Kupffer cells and in the liver cells toward the central vein.

In previous studies by Bensley and Woerner³⁰ the suggestion was made that the alpha cells secrete a substance concerned with fat metabolism and that the oxidation of fat depends not only on the presence of this substance but also on available oxidizable sugar. They had been able to make an extract of alpha cells and to obtain with it a decrease in the fat content of the liver. The dose of alpha cell extract, computed in terms of grams of fresh pancreas per kilogram of body weight per day, was about half the dose of alcoholic extract of pancreas (lipocain) used by Diagstedt and his co-workers.²⁶ The ingenious device for maintaining continuous intravenous injection in such small animals as the guinea pigs used in these experiments of Woerner and Bensley is described in another paper.³¹

(e) Activity of Islands of Langerhans. It long has been known that a normal person deprived of carbohydrate for a period of several days responds to a dose of sugar with a diabetic type of blood sugar-time curve. The phenomenon has been interpreted by some as indicating that quiescence of the pancreatic islands is induced by the small demand for insulin. By others it is regarded as resulting from changes in the function of the liver. Both mechanisms probably are involved, but

30 Bensley, S. H., and Woerner, C. A., cited by Woerner²⁹

31 Woerner, C. A. A Simplified Method for Continuous Intravenous Injection into Small Animals, *J. Lab. & Clin. Med.* **24** 963-970 (June) 1939

supporting the former is an observation of Haist, Ridout and Best³² These authors reported as follows to the American Physiological Society at the annual meeting in Toronto

In order to investigate the effect of dietary changes on the insulin content of pancreas it is necessary to have available, first, a method which consistently gives a maximal yield of anti-diabetic substance, second, a method of testing insulin which gives accurate results with the amount of active material available, and thirdly, a test animal which will consistently eat the diets provided and whose pancreas can be completely removed without undue difficulty With regard to the first requirement the method recently described by Scott and Fisher [Am J Physiol **121** 253, 1938], with very slight modifications, is satisfactory The mouse method of assay of insulin, using from 200 to 300 mice for each sample of insulin-containing extract, has been found to give remarkably consistent results [White rats of the Wistar strain eat the diets which have been used and all the pancreatic tissue can readily be removed when survival of the animals is not desired The pancreatic tissue from 10 rats provides from 20 to 30 units of insulin, an amount which is more than adequate for the test on 300 mice]

Utilizing these procedures, we have studied the changes in insulin content of rat pancreas under a variety of dietary conditions It has been found that starvation produces a very definite decrease in the insulin content of pancreas Diets very rich in fat cause a marked diminution in insulin content Diets rich in carbohydrate [do not lead to a decrease in the insulin content]

Bearing indirectly on the question whether deprivation of carbohydrate depresses (temporarily) the production of insulin by the normal pancreas are the respiratory quotients of normal persons and the calculations of carbohydrate utilization therefrom Such determinations have been reported by Johnston, Sheldon and Newburgh,³³ of Ann Arbor, Mich The subjects, 2 normal men, were previously on a low intake of calories and carbohydrate They failed to oxidize all of the intake of carbohydrate If, however, the diets were adequate and contained more carbohydrate, what was ingested could be accounted for by oxidation The impairment of the ability to oxidize carbohydrate appeared to be related to the degree of depletion of previously existing stores of glycogen Before this, Cori and Cori³⁴ had found that rats which had fasted forty-eight hours oxidized relatively less dextrose and deposited relatively more glycogen in their muscle, and Johnston and his associates³³ commented that under conditions of glycogen deprivation it is more important apparently to replenish the carbohydrate store than to use incoming carbohydrate for fuel In our opinion these results are exactly what would be expected from limitation of the supply

32 Haist, R E, Ridout, J H, and Best, C H Diet and the Insulin Content of Pancreas, Am J Physiol **126** 518-519 (July) 1939

33 Johnston, M W, Sheldon, J M, and Newburgh, L H The Utilization of Carbohydrate in Human Undernutrition, J Nutrition **17** 213-222 (March) 1939

34 Cori, C F, and Cori, G T, cited by Johnston, Sheldon and Newburgh³³

of insulin, since insulin seems not to be required for the formation of muscle glycogen but is necessary for a high rate of oxidation of carbohydrate

An observation which bears on the capacity of the diabetic pancreas to export insulin is contained in a paper by Labbé,³⁵ who found the Staub-Traugott reaction to be absent in patients with diabetes. Staub³⁶ and Traugott³⁷ independently, and before them, in Baltimore, Hamman and Hirschman,³⁸ showed that a second dose of dextrose given by mouth to a normal human subject an hour or so after a preliminary dose had little, if any, elevating effect on the level of the blood sugar. The absence of effect from the second dose is interpreted as meaning that the first dose activated the mechanism for utilizing incoming sugar. The activation is supposed to depend on stimulation of the pancreatic islands.¹ This Staub-Traugott (Hamman-Hirschman) phenomenon could be obtained by Labbé with normal persons but was not apparent with diabetic patients. His explanation is that in diabetes the pancreas must be incapable of exporting more than a certain minimum of insulin.

The paper of Labbé,³⁵ containing the brief report just cited, was one of the last in the extensive bibliography of this distinguished clinician. Marcel Labbé (1870-1939) has been the leading clinical authority in France on diseases of metabolism and nutrition. An account of his notable contributions is contained in the many obituaries that appeared this year in French journals of medicine.³⁹

Also bearing on the subject of the capacity of the diabetic pancreas to export insulin is an important and long delayed contribution from the Connaught (Insulin) Laboratories in Toronto, Canada. It concerns the insulin content of pancreas removed at necropsy from the bodies of persons who died with diabetes. Analyses for insulin were made on 14 normal and 18 diabetic pancreases by Scott and Fisher.⁴⁰ The average value in the normal organs was 1.7 international units per gram (173 units per pancreas). The value 1.7 is in good agreement with the average value of insulin (1.8) obtained in analysis of the pancreas

35 Labbé, M. La réaction de Traugott-Staub. Essai d'application à l'alimentation des diabétiques, *Ann de med* **44** 393-405 (Dec.) 1938

36 Staub, H. Bahnung im intermediären Zuckerstoffwechsel, *Biochem Ztschr* **118** 93-102, 1921

37 Traugott, K. Ueber das Verhalten des Blutzuckerspiegels bei wiederholter und verschiedener Art enteraler Zuckerzufuhr und dessen Bedeutung für die Leberfunktion, *Klin Wchnschr* **1** 892-894 (April) 1922

38 Hamman, L., and Hirschman, J. I. Studies on Blood Sugar. IV Effects upon the Blood Sugar of the Repeated Ingestion of Glucose, *Bull Johns Hopkins Hosp* **30** 306-308, 1919

39 Bezançon, F. Marcel Labbé, 1870-1939, *Ann de med* **46** 89-94 (July) 1939

40 Scott, D. A., and Fisher, A. M. The Insulin and the Zinc Content of Normal and Diabetic Pancreas, *J Clin Investigation* **17** 725-728 (Nov.) 1938

of the mature cow. In the diabetic human pancreas the average value was 0.4 unit per gram (less than 40 units per pancreas). What doubt remains regarding the primary significance of the pancreas in clinical diabetes should be stilled if the results of analyses of more material agree with these.

Sex Incidence—No one study has explained the unusual frequency of diabetes among Jews, nor the relatively high proportion of females among diabetic Jews. Rudy and Keeler⁴¹ added further statistical data and compared observations made on more than 1,000 Jewish diabetic patients in the Beth Israel Hospital of Boston with other data, especially those of Joslin. Rudy and Keeler found the incidence of familial diabetes (diabetes in brothers, sisters or first cousins) to be from four to six times as high in diabetic as in nondiabetic Jews and that of hereditary diabetes (diabetes in parents, grandparents, aunts

TABLE 2—*Sex of Newly Registered Diabetic Patients in the Mayo Clinic*

Year	Male*		Female	
	Patients	Percentage	Patients	Percentage
1924	181	52.5	164	47.5
1925	209	53.2	184	46.8
1926	177	51.5	167	45.5
1927	256	57.1	192	42.9
1928	188	52.4	171	47.6
Total	1,011	53.5	878	46.5
1935	308	55.9	243	44.1
1936	385	56.6	295	43.4
1937	438	57.1	329	42.9
Total	1,131	56.6	867	43.4

* The percentage of males among all newly registered patients (those not previously seen) in the Mayo Clinic has been close to 50 for many years. In 1938 it was 48.6.

and uncles) to be higher in the younger age groups. They also noted that Jewish females with diabetes outnumbered Jewish males with the disease in a ratio of nearly 2:1. This sex ratio is much higher than that reported by Joslin for all diabetic patients and may provide an explanation for the fact that the number of female patients with diabetes exceeds the number of male patients with the disease in clinics in Boston and New York, where the Jewish population is relatively large. Such preponderance of females over males has not been observed among the diabetic patients who come to the Mayo Clinic, where the clientele is largely derived from rural regions or smaller towns. In our experience males predominate, and their predominance seems to be on the increase (table 2). The incidence of Jews among new diabetic patients coming to the clinic runs about 12 per cent. In 1938 it was 12.8 per cent.

⁴¹ Rudy, A., and Keeler, C. E. Studies on Heredity in Jewish Diabetic Patients, *New England J. Med.* **221**: 329-332 (Aug. 31) 1939.

The predominance of females with diabetes over males with this disease in the experience of the Metropolitan Life Insurance Company⁴² may also be influenced by an undue weighting with Jews. The section of the population represented in the policyholders of this company is industrial and therefore mostly urban.

Diagnosis—(a) *Exton-Rose Test* For some years Exton's simplified tolerance test, the two dose—one hour test, has been in use in the Mayo Clinic as one of several means of diagnosis in cases in which diabetes was suspected. The collected material has now been examined by Matthews, Magath and Berkson,⁴³ who selected for statistical analysis the results obtained with this test in 117 subjects called normal, 304 patients with diabetes mellitus and 70 patients with renal glycosuria. Results obtained with the test in cases in which any disease other than diabetes was noted were eliminated. In all cases the clinical diagnoses had been made by physicians who had special experience in diabetes. These physicians gave the tests consideration, but they based their diagnoses on all the information obtainable and not on the tests alone. Indeed, in interpreting the tests for purposes of diagnosis other criteria were used than those developed in this statistical examination.

From the study of Matthews and his associates,⁴³ the correlation between the clinical diagnosis and the earlier criteria for interpreting the Exton-Rose test appears to be much less satisfactory than the correlation which can be observed between the clinical diagnosis and the simple criterion provided by the value for the blood sugar one hour after the first dose of dextrose is ingested. When subjects who had a concentration of blood sugar of less than 0.158 Gm per hundred cubic centimeters at the hour were designated as nondiabetic, and those with readings at or more than 0.180 Gm as diabetic, all but 25 of the 364 patients had values of blood sugar in one of the two groups, and the laboratory designation agreed with the diagnosis of the physician. Of the 25 persons with values of blood sugar at the hour between the critical levels named, i. e., between 0.158 and 0.179 Gm, 6 patients were called nondiabetic by the clinician, and 19 were considered as having exceedingly mild diabetes. This incidence of doubtful designation not only was smaller than that obtained by use of earlier criteria for

42 Dublin, L. I., and Lotka, A. J. *Twenty-Five Years of Health Progress. A Study of the Mortality Experience Among the Policyholders of the Metropolitan Life Insurance Company, 1911 to 1935*, New York, Metropolitan Life Insurance Company, 1937.

43 Matthews, M. W., Magath, T. B., and Berkson, J. *The One Hour—Two Dose Dextrose Tolerance Test (Exton-Rose Procedure)*, J. A. M. A. **113** 1531-1537 (Oct 21) 1939.

interpreting the Exton-Rose test but was much smaller than that found by Matthews⁴⁴ using any criteria heretofore proposed for interpreting the so-called standard three hour—one dose dextrose tolerance test

(b) Significance of Hyperglycemia Not Accompanied by Glycosuria It is a common practice to regard a fasting value for blood sugar of more than 0.120 Gm per hundred cubic centimeters associated with glycosuria as diagnostic of diabetes mellitus, but what about hyperglycemia with no glycosuria? Davidson⁴⁵ reported 17 examples of this. No sugar appeared in the urine even when dextrose was administered for a one dose—three hour tolerance test, in the course of which the blood sugar rose to values between 0.200 and 0.300 Gm per hundred cubic centimeters. Six of the patients were children. We have encountered an occasional case of this type and have attributed the condition to abnormal elevation of the renal threshold. That the abnormality occurs with sufficient frequency to have enabled one observer to report 17 examples and to comment, as Davidson⁴⁵ did, that he had encountered several score of equally striking cases is startling, to say the least. In Davidson's opinion, such hyperglycemia may initiate and maintain metabolic disturbances that are susceptible to correction by treatment with a diabetic diet.

The better known abnormality of the renal threshold for dextrose is renal dextrosuria (renal diabetes), in which the threshold for sugar is depressed below normal so that sugar is excreted by the kidneys from normal or even abnormally low levels of blood sugar. A review of Joslin's experience of thirty-five years with nondiabetic glycosuria was recently reported by Marble, Joslin, Dublin and Marks⁴⁶. They defined "renal glycosuria" as denoting constant glycosuria *even in the fasting state* (when values for blood sugar are less than 0.120 Gm per hundred cubic centimeters), postprandial values for blood sugar of less than 0.170 Gm per hundred cubic centimeters and an absence of diabetic symptoms. In none of 67 cases satisfying the criterion of renal glycosuria in this limited sense did diabetes mellitus develop later. However, of a total of 1,946 patients with all types of nondiabetic glycosuria, true diabetes later developed in 193, or 9.9 per cent. The entire series included 4 cases of pentosuria and 1 case of fructosuria. The statement is made that often in cases of pentosuria and fructosuria

44 Matthews, M. W. A Study of the One Dose—Three Hour (Standard) and Two Dose—One Hour (Exton-Rose) Glucose Tolerance Test, Thesis, University of Minnesota Graduate School, 1939.

45 Davidson, C. F. Hyperglycemia Without Glycosuria Associated with Disturbances in Metabolic Processes, *Endocrinology* **24** 542-549 (April) 1939.

46 Marble, A., Joslin, E. P., Dublin, I. I., and Marks, H. H. Studies in Diabetes Mellitus. VII. Nondiabetic Glycosuria, *Am. J. M. Sc.* **197** 533-556 (April) 1939.

the diagnosis is first diabetes, then renal glycosuria, and the suggestion is made that whenever melituria is proved not to be diabetic the type of sugar should be identified

Prognosis—(a) *Course of Diabetes in Children* An encouraging survey of the condition of children with diabetes is reported from Los Angeles by Grishaw, West and Smith⁴⁷ The status of 315 of a series of 341 diabetic children was known Among them were 86 in whom diabetes had developed prior to January 1928 and who thus had lived ten years or more since its development Twenty-five per cent of the 86 had died, but only 3 of the deaths had occurred since 1930 The mortality for the 219 children exposed less than ten years was 9.2 per cent The cause of half of all deaths was coma, and in consequence of improving methods of preventing coma better results can be expected in the future Among nonfatal complications, retinitis was found in only 2 of all the children and cataract in only 1 Pulmonary tuberculosis was noted in only 1 and arteriosclerosis in only 1

The intelligence of diabetic children has impressed every one who has had experience in treating many of these little patients Intelligence ratings were obtained for 62 unselected children of the group studied by Grishaw and his associates⁴⁷ The ratings were well in advance of normal, 42.1 per cent were more than 110 compared with 20.6 per cent of Teiman's normal, unselected children Only 10.5 per cent of the ratings were less than 90, compared with 19.4 per cent for Teiman's unselected children

(b) *Prejudice Against Employment of Patients with Diabetes* A commendable protest was made by Lawrence and Madders⁴⁸ at the discrimination by employers against persons with diabetes This attitude is a survival of preinsulin days and now is unfair and unjust A formal survey of 100 employed diabetic persons revealed that 85 per cent of them when stabilized on insulin lost no time from their work Lawrence and Madders concluded that most diabetic persons when adequately treated are good employees from the point of view of health

The modern aim in the treatment of diabetes, as is well explained in a recent bulletin of the Metropolitan Life Insurance Company,⁴⁹ is to restore the patient and then to keep him as a useful and productive citizen in the community This objective is well on the way to being

47 Grishaw, W. H., West, H. F., and Smith, B. Juvenile Diabetes Mellitus Arch Int Med 64 787-799 (Oct) 1939

48 Lawrence, R. D., and Madders, K. The Employment of Diabetics, Brit M J 2 1076-1077 (Nov. 26) 1938

49 Working Capacity of Diabetics, Statist Bull., Metropolitan Life Insur. Co 20 7-10 (Oct) 1939

realized, but both doctors and patients must help in attaining it. Every patient with diabetes who is regularly employed not only is himself the gainer but thereby establishes a reputation which helps to overcome the prejudice of employers against other diabetic persons.

INSULIN

Choice of Insulin—Although dissent continues to find expression, the opinion prevails that the use of protamine zinc insulin is desirable in most cases of diabetes. It is widely recognized, however, that such an insulin can be used successfully only for patients with the milder forms of the disease and should be combined with some quicker acting insulin for patients with diabetes of severity. The American, English and German experience with protamine zinc insulin has been cited extensively in our previous reviews.⁵⁰ The French experience has been reported by Boulin and his associates.⁵¹ Boulin himself⁵² reported separately on the results of the use of this insulin in 100 cases.

The long duration of action of large doses of protamine zinc insulin has been emphasized by Allen,⁵³ who demonstrated, in animal experiments involving amputations, that the continued effect is due to retention at the site of injection for periods up to sixty-two hours. An interesting review of the various substances, protamines, histones and so forth, effective in retarding the action of insulin was made by Vartiainen and Bastman.⁵⁴ Sandberg and Brand⁵⁵ had suggested that insulin was bound to arginine or guanidine groups in most of the substances which when added to insulin retard its activity. Sandberg and Brand, experimenting with arginine alone, found that it caused a retardation comparable to that obtained with protamine. The dose of arginine necessary approximated 100 mg per kilogram.

Another suggestion for retarding the action of insulin is that of Feinblatt,⁵⁶ who added hexamethylenetetramine (methenamine) in the

50 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch Int Med* **61** 297-365 (Feb.) 1938. Wilder and others.¹ Wilder and Wilbur, footnotes 15 and 23.

51 Boulin, R., Ullmann, M., Mallet, R., and Bour, H. L'insuline-protamine zinc dans le traitement du diabète sucré, *Ann d'endocrinol* **1** 270-292 (July) 1939.

52 Boulin, R. Le traitement du diabète sucré par l'insuline-protamine-zinc (statistique de 100 cas), *Presse med* **47** 541-544 (April 12) 1939, abstracted, *Bull et mem Soc med d'hôp de Paris* **55** 41-43 (Jan 30) 1939.

53 Allen, F. M. Tolerance and Toxicity of Insulin. III. Protamine and Zinc Compounds, *Ann Int Med* **12** 1870-1885 (May) 1939.

54 Vartiainen, J., and Bastman, L. The Retardation of the Effect of Insulin by Means of Arginine, *Acta med Scandinav* **98** 318-327, 1939.

55 Sandberg and Brand, cited by Vartiainen and Bastman.⁵⁴

56 Feinblatt, H. M. Juvenile Diabetes Mellitus (A Comparative Study of Standard Insulin, Crystalline Insulin, Protamine Insulin and Hexamine Insulin), *J Lab & Clin Med* **24** 337-341 (Jan.) 1939.

amount of $\frac{1}{4}$ gram (0.06 Gm) to 1,000 units of insulin. The resulting mixture is soluble but precipitates at the p_H of the tissue fluids. The claim is made that this "hexamine insulin" is not irritating and is as stable as protamine zinc insulin. The protection provided against ketonuria is as striking as that with protamine zinc insulin, and shock from overdose (collapse reaction) responds immediately to carbohydrate.

Almost acrimonious discussion has centered, during the past year, around the original claims of one of the American manufacturers of insulin that solution of zinc insulin crystals, recently made available commercially, possesses a retarded action comparable to that with protamine zinc insulin. This claim was supported at first by several clinical reports, but from personal experience⁵⁷ and from the reports of Marble and Vartiainen⁵⁸ and Jackson and Boyd⁵⁹ the claim in question definitely is discredited. Jackson and Boyd⁵⁹ conducted their clinical experiments under conditions with regard to control which were superior to those imposed by any investigators or clinical observers who reported prolongation of action for solution of zinc insulin crystals, and they concluded that no distinction need be made in regard to the qualitative and the quantitative effects of equal unitages between crystalline and amorphous insulin or between the corresponding products of various manufacturers. Marble and Vartiainen⁵⁸ reached similar conclusions, although they found that insulin of the crystalline type seemed to act slightly longer and that it was a desirable insulin from the standpoint of high purity. In rapidity of action it proved exactly comparable to amorphous insulin. Ricketts and one of us (Wilder⁵⁷) obtained blood sugar-time data after injection of single doses of two types of insulin, given without food, in a carefully selected group of diabetic patients. The nature of the two types of insulin was undisclosed until after the conclusion of the experiments. The data failed to reveal material differences either in rapidity or in duration of action between these types of insulin. One of them was a solution of amorphous (regular) insulin and the other a solution of zinc insulin crystals supplied by the Eli Lilly Company. The average of all data obtained with a preparation of zinc insulin crystals (Stearns) pur-

57 Ricketts, H. T., and Wilder, R. M. Solutions of Amorphous Insulin and Solutions of Zinc Insulin Crystals. Clinical Studies of the Comparative Speed and Duration of Action, *J. A. M. A.* **113**:1310-1312 (Sept. 30) 1939.

58 Marble, A., and Vartiainen, J. Crystalline Insulin, *J. A. M. A.* **113**:1303-1309 (Sept. 30) 1939.

59 Jackson, R. L., and Boyd, J. D. Relative Efficiency of Commercial Forms of Insulin, *Proc. Soc. Exper. Biol. & Med.* **41**:15-16 (May) 1939.

chased on the open market showed a slight but statistically significant prolongation of action, although no difference in speed of action, when compared with the average of all data obtained after injection of amorphous insulin. This difference was not apparent in all patients, and it was concluded that the slight difference was probably of no clinical importance.

The content of zinc in the various batches of insulin used in the experiments of Ricketts and Wilder⁵⁷ was small and not comparable to that in the preparations of crystalline insulin, containing more zinc, with which one of us (Wilder⁶⁰) previously reported retardation of action. That addition of zinc to insulin retards its action is now well known.

Insulin Allergy—As was stated by Marble and Vaitiainen,⁵⁸ crystalline insulin should give rise to fewer allergic reactions than amorphous insulin. However, at present the market preparations of amorphous insulin (regular insulin) are of a high degree of purity, and allergic reactions from them are much less frequent than formerly. Indeed, severe allergic reactions have become unusual. One was reported this year by Ulrich, Hooker and Smith⁶¹ in a nondiabetic person given insulin to stimulate appetite. A generalized erythematous rash developed, with chill, substernal pain and low blood pressure. Similar reactions were obtained with insulins of different origin (beef and pork), also with crystalline insulin, although the reaction with crystalline insulin of beef origin were less severe. Effective desensitization was obtained by intradermal administration of minute doses of insulin, followed by subcutaneous injection of progressively increasing doses.

Rathery and associates⁶² also described a severe anaphylactic reaction. Their patient had diabetes. She received insulin in 1932. This at first was tolerated, but after two months it caused urticaria, and its use was discontinued. In 1938, insulin was administered again, and ten minutes later the skin of the entire upper half of the body showed flushing and tumefaction. Subsequently a much more severe reaction was obtained with a crude preparation of insulin given intradermally in a dose of 0.05 cc. A minimal reaction followed the administration of a solution of crystalline insulin. From these observations and from the results of an experimental study on animals desensitized previously

60 Wilder, R. M. Clinical Investigations of Insulins with Prolonged Activity, *Ann Int Med* **11** 13-30 (July) 1937.

61 Ulrich, H., Hooker, S. B., and Smith, H. H. Allergic Reaction to Insulin, *New England J Med* **221** 522-524 (Oct 5) 1939.

62 Rathery, F., Bargeton, D., Maschas, H., and Tuijaf, J. Insuline et anaphylaxie, *Bull et mém Soc med d hôp de Paris* **55** 580-588 (April 10) 1939.

with the serum of this patient, Rathery and his colleagues concluded that contaminants of the insulin rather than the insulin itself were responsible for the reactions

Roth and Rynearson⁶³ reported the successful use of histaminase in the treatment of patients with insulin allergy of moderate severity. Such is the allergy in which hard, tender, red areas up to 6 inches (18 cm) in diameter develop at the sites of injection and persist for several days. One patient took 3 tablets of histaminase by mouth three times daily, and at the end of six days the local reactions had disappeared. The suggestion is promising, but preparations of histaminase of assured activity have been obtainable only recently.

Regarding reaction at the site of injection of protamine zinc insulin, which occurred in 16 per cent of their cases, Kern and Langner⁶⁴ stated that such reactions probably are not due to sensitization to protamine, because 104 patients treated with protamine zinc insulin and 8 allergic nondiabetic patients who were found by cutaneous tests to be sensitive to salmon muscle protein had negative intracutaneous reactions on tests with a solution of protamine. The statement is in keeping with the present knowledge that protamines have no antigenic properties. The reactions appeared to be caused by errors in the technique of injection. However, 2 of the patients became sensitive to insulin five and eight days, respectively, after protamine zinc insulin was substituted for soluble insulin in the treatment of their diabetes, and the suggestion is made that the sensitivity to insulin was a result of the more prolonged action of the antigen (insulin) in the course of its slower absorption in the precipitated state.

Levels of Control of Glycosuria—Opinion is divided sharply as to the degree of control desirable when patients are receiving protamine zinc insulin. Boyd and Jackson⁶⁵ expressed the belief that the regimen should be directed toward the conservation of the patient's resources in their entirety and that a regimen which requires or condones glycosuria even of a mild degree cannot be considered favorable for the patient's ultimate welfare. Several other writers have expressed similar opinions. On the other hand, the danger inherent in attacks of hypo-

63 Roth, G. M., and Rynearson, E. H. Histamine and Histaminase in the Treatment of Allergic Reactions to Insulin, *Proc. Staff Meet., Mayo Clin.* **14**: 353-358 (June 7) 1939.

64 Kern, R. A., and Langner, P. H., Jr. Protamine and Allergy. I. Nature of the Local Reactions After Injection of Protamine Zinc Insulin, II. Induction of Sensitivity to Insulin by Injections of Protamine Zinc Insulin, *J. A. M. A.* **113**: 198-200 (July 15) 1939.

65 Boyd, J. D., and Jackson, R. L. Levels of Control in the Treatment of Diabetes Mellitus, *J. A. M. A.* **111**: 906-909 (Sept 3) 1938.

glycemia, emphasized again by Shei11 and MacKay,⁶⁶ has led many authorities to oppose such rigid control. Their position is strengthened by the obviously improved state of health of patients formerly treated more rigidly with regular insulin. A variety of methods have been suggested for overcoming the obvious difficulty in preventing post-prandial excretion of sugar when protamine zinc insulin is depended on exclusively and given once daily. Some writers have recommended that there be six meals daily. Others start the day with little carbohydrate and give relatively more in the afternoon and evening. A careful study of the problem by Tolstoi and Weber,⁶⁷ of the Cornell Clinic, led them to conclude that "for patients treated with protamine zinc insulin the guiding factor of satisfactory treatment should be the maintenance of weight, freedom from symptoms and absence of ketone bodies in the urine. Glycosuria is desirable, as it affords freedom from reactions." We incline to agree with this opinion but would hesitate to accept the degree of glycosuria permitted by Tolstoi and Weber and usually succeed in avoiding daily excretion of more than 10, or at most, 20 Gm of sugar by giving some regular (or crystalline) insulin with the protamine zinc insulin in all cases in which more than 20 or 30 units of insulin is required. The protamine zinc insulin and regular insulin are mixed in one syringe according to the method described by Lawrence and Graham mentioned in our last year's review.¹ We find this procedure to be highly satisfactory.

MONOGRAPHS ON DIABETES AND INSULIN

Of interest and to be recommended to the student of diabetes are the following monographs published in 1938 or 1939. "Insulin: Its Chemistry and Physiology," by Hans F. Jensen,⁶⁸ "Die Diät- und Insulinbehandlung der Zuckerkrankheit für Studierende und Aerzte," by Franz Depisch,⁶⁹ and the Goulstonian Lectures on the mechanism of diabetes mellitus, by H. P. Himsworth.⁷⁰

66 Shei11, J. W., and MacKay, E. M. Deleterious Effects of Experimental Protamine Insulin Shock, *Arch. Int. Med.* **64**: 907-912 (Nov.) 1939.

67 Tolstoi, E., and Weber, F. C., Jr. Protamine Zinc Insulin. A Metabolic Study, Treatment in Two Cases of Severe Diabetes by Equally and Unequally Divided Diets, with Comments on Criteria for Treatment, *Arch. Int. Med.* **64**: 91-104 (July) 1939.

68 Jensen, H. F. *Insulin: Its Chemistry and Physiology*, New York, Oxford University Press, 1938.

69 Depisch, F. *Die Diät- und Insulinbehandlung der Zuckerkrankheit für Studierende und Aerzte*, ed. 2, Berlin, Julius Springer, 1939.

70 Himsworth, H. P. The Mechanism of Diabetes Mellitus, *Lancet* **2**: 1-6 (July 1) 1939, II The Control of the Blood-Sugar Level, *ibid.* **2**: 65-68 (July 8), 118-122 (July 15) 1939, III Human Diabetes Mellitus, *ibid.* **2**: 171-176 (July 22) 1939.

HYPERINSULINISM AND GLYCOGENOSIS

A number of recent reports of insular tumor associated with paroxysmal hypoglycemia have come to our attention⁷¹ A discussion of the pathologic characteristics of insular tumors is given by Laidlow,⁷² who designates them as "nesidioblastomas"

An investigation by Seckel^{71c} of the rate of postmortem hepatic glycogenolysis in 2 fatal cases, in one of which an insular carcinoma was found, fills a gap in present knowledge When one of us (Wilder), with Allan, Power and Robertson,⁷³ described the original case of pancreatic tumor with hyperinsulinism, attention was called to a very high glycogen content in the liver, and it was suggested that an equally unusual case previously reported by Parnas and Wagner⁷⁴ might be one of a similar condition The case of Parnas and Wagner, in which hepatomegaly, hypoglycemia, ketonuria and retardation of growth occurred in a 9 year old child, is now regarded as the first case of glycogenosis (glycogen disease, von Gierke's disease) to be described It was learned later that a fundamental abnormality in glycogenosis is inhibition in vivo and post mortem of hepatic glycogenolysis, and in discussions of its genesis hyperinsulinism, time and again, has been suggested as responsible Not determined, however, either in the original case or in any of the numerous cases of hyperinsulinism which subsequently have been reported, was whether postmortem glycogenolysis was abnormal in hyperinsulinism This, Seckel^{71c} investigated in his cases One was an instance of carcinoma of the islands of Langerhans, the other, a case of "neurogenic hyperinsulinism," in which a massive fibroma was found on the dome of the right lobe of the liver Comparatively high contents of glycogen were encountered

71 (a) Jirasek, A, and Postranecky, O Un cas d'adenome des ilots de Langerhans, diagnostic, operation, guerison, *Presse med* **46** 671-672 (April 27) 1938 (b) Parade, G W, and Kindler, K Inselzellenadenom, durch Operation geheilt, *Klin Wchnschr* **17** 810-813 (June 4) 1938 (c) Fraser, R, Macley, W S, and Mann, S A Hyperinsulinism Due to a Pancreatic Islet Adenoma, *Quart J Med* **7** 115-135 (Jan) 1938 (d) Malamud, N, and Grosh, L C, Jr Hyperinsulinism and Cerebral Damage Report of a Case Due to an Islet Cell Adenoma of the Pancreas, *Arch Int Med* **61** 579-599 (April) 1938 (e) Seckel, G Postmortem Hepatic Glycogenolysis in Hyperinsulinism and Glycogen Disease, *J Clin Investigation* **18** 723-731 (Nov) 1939 (f) Campbell, W R, Gradam, R R, and Robinson, W L Islet Cell Tumor of the Pancreas, *Tr A Am Physicians* **54** 304-319, 1939

72 Laidlow, G F Nesidioblastoma, the Islet Tumor of the Pancreas, *Am J Path* **14** 125-134 (March) 1938

73 Wilder, R M, Allan, F N, Power, M H, and Robertson, H E Carcinoma of the Islands of the Pancreas Hyperinsulinism and Hypoglycemia, *J A M A* **89** 348-355 (July 30) 1927

74 Parnas, J K, and Wagner, R, cited by Seckel^{71c}

in the liver and muscle in both cases, but postmortem hepatic glycogenolysis was approximately normal or only slightly decreased. Seckel's conclusion is that neither form of "hyperinsulinism" can be identified with typical glycogenosis and that typical glycogenosis cannot, therefore, originate from either form of "hyperinsulinism."

An important review of the literature on glycogenosis was published recently by van Creveld,⁷⁵ who with Snapper⁷⁶ gave the first clinical report of a case of the disease in 1928.

DIABETES INSIPIDUS

The important studies of Fisher, Ingram and Ranson, of Northwestern University Medical School, now are assembled in a monograph.⁷⁷ The work of these authors seems to have established that the posterior lobe of the pituitary is an endocrine gland with an antidiuretic role in water metabolism and to have defined diabetes insipidus as a syndrome of pituitary insufficiency caused by diminution or absence of the antidiuretic hormone of the posterior lobe. When the posterior lobe of the pituitary body is extirpated or undergoes atrophy as a result of a lesion of the hypothalamus in which the supraoptical hypophyseal tracts are interrupted, diabetes insipidus follows.

Swann and Penner⁷⁸ conducted experiments which throw into relief the significance in diabetes insipidus of the intake of certain salts, notably sodium chloride and sodium bicarbonate. Postoperative diabetes insipidus in the rat seldom results in the daily exchange of 500 cc of fluid per kilogram of body weight, but on administration of sodium chloride amounts of fluid exceeding 1,000 cc per kilogram per day are not uncommon. Such quantities are equal in weight to the animal's body. Recovery from posthypophysectomy diuresis is usually noted, but diuresis from administration of salt after hypophysectomy, once initiated, continues unchecked. Posterior pituitary prevents these saline aggravations of the diabetes. Fasting and diets low in sodium chloride suppress but do not entirely prevent the diabetes. The suggestion is made by Swann and Penner⁷⁸ that the changes in the water metabolism in diabetes insipidus are secondary to changes

75 van Creveld, S. Glycogen Disease, *Medicine* **18** 1-128 (Feb.) 1939.

76 van Creveld and Snapper, cited by van Creveld.⁷⁵

77 Fisher, C., Ingram, W. R., and Ranson, S. W. Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance. A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

78 Swann, H. G., and Penner, B. J. The Effect of Salts on the Diabetes Insipidus Following Posthypophysectomy in the Rat, *Endocrinology* **24** 253-259 (Feb.) 1939, Sodium Chloride and Diabetes Insipidus, *Am J Physiol* **126** 341-346 (June) 1939.

in the metabolism of sodium chloride Swann and Johnson⁷⁹ observed further that thyroidectomy interfered only slightly, if at all, with an existing salt-aggravated diabetes insipidus in the rat, even when it caused the oxygen consumption to decrease 44 per cent Clinically it is generally recognized that intake of sodium chloride affects significantly the severity of diabetes insipidus In some few cases satisfactory control can be obtained by restriction of salt alone In many more the effectiveness of posterior pituitary may be improved by restriction of salt

It is reported from France by Decourt and his associates⁸⁰ that the water content of erythrocytes in cases of diabetes insipidus is increased from 4 to 6 per cent by injections of a solution of posterior pituitary This increase occurs without any appreciable hydremia of the plasma or parallel increase of the chlorides of the cells The subject demands further study The observation suggests that one effect of posterior pituitary is on the capacity for binding water of the intracellular colloids of the tissues in general

A case of diabetes insipidus reported by Bernstein and co-workers⁸¹ is of interest in that necropsy revealed the hypophysis and infundibulum to be invaded by metastatic carcinoma with complete sparing of the hypothalamus

Diabetes insipidus and diabetes mellitus are rarely encountered in the same case A review of the literature by Greene and Gibson⁸² revealed only 20 examples Greene and Gibson added another in which pregnancy was associated with the simultaneous development of both diabetes mellitus and diabetes insipidus Injection of a solution of posterior pituitary induced labor Another instance of the coexistence of diabetes mellitus and diabetes insipidus was reported by Rutledge and Rynearson⁸³ In the same report attention was again called to

79 Swann, H G, and Johnson, P E Thyroid Function in Diabetes Insipidus in the Rat, *Endocrinology* **24** 397-403 (March) 1939

80 Decourt, J, Guillaumin, C O, and Bernard, J Variations de l'hydiemie globulaire et plasmatique sous l'influence de l'extrait post-hypophysaire dans deux cas de diabete insipide, *Presse med* **47** 795 (May 24) 1939

81 Bernstein, M, Moore, M T, and Fishback, D B Diabetes Insipidus as a Sign of Metastatic Involvement of the Supraopticohypophysial System, *Arch Int Med* **62** 604-617 (Oct) 1938

82 Greene, J A, and Gibson, R B Co-Existence of Diabetes Mellitus and Diabetes Insipidus, *J Lab & Clin Med* **24** 455-457 (Feb) 1939

83 Rutledge, D I, and Rynearson, E H Diabetes Insipidus I Co-Existence of Diabetes Mellitus and Diabetes Insipidus, II Treatment by Insufflations of Powdered Posterior Pituitary Substance, *Proc Staff Meet, Mayo Clin* **14** 441-446 (July 12) 1939

the value of insufflation of desiccated posterior pituitary in the treatment of diabetes insipidus. This type of therapy received attention in an earlier review¹⁵

GOUT

Gout is included among the subjects considered in the fifth "rheumatism review" prepared by the editorial committee of the American Rheumatism Association⁸⁴. A sixth "rheumatism review" is scheduled for publication early in 1940. These extensive papers cover the subject of gout more adequately than we have space to do and are accompanied by critical editorial comments. Since they are readily available to most of our readers, those interested are referred to them.

Little progress has been made in the study of gout. The etiology of this disease is still obscure, and even the established causes are ill defined. The diagnosis is attended with uncertainty in many cases, recent papers on the beneficial effect of purine-free diets and diets low in fat and high in carbohydrate represent restatements, for the most part, of what has been known for many years. The subject received editorial comment in the *Lancet*⁸⁵. The lack of progress is attributed largely to lack of interest. The whole field lies fallow, awaiting some such discovery as occurred in relation to diabetes and pernicious anemia.

Worthy of comment is a paper by Price,⁸⁶ who again called attention to the provocation of gout by diuresis induced with salyrgan. Five cases were described in which there was a history of gout and in which attacks of gout followed administration of salyrgan. As salyrgan usually is given to patients with cardiac failure, the outcome of the complication is generally unfortunate. The suggestion is offered that either gout develops only after forced diuresis in a patient already in the terminal stages of cardiac failure or the attack has some deleterious action on the heart. In either case the wisdom of using mercurial diuretics for patients giving a history of gout is questioned.

OBESITY

A near record in therapeutic reduction of weight was reported by Short⁸⁷. His patient, a woman aged 32 years, was reduced from 395½

84 Hench, P. S., Bauer, W., Dowson, M. H., Hall, F., Holbrook, P., and Key, J. A. The Problem of "Rheumatism" and Arthritis. Review of American and English Literature for 1937 (Fifth Rheumatism Review, Part II), *Ann Int Med* **12** 1295-1374 (Feb.) 1939.

85 Gout, editorial, *Lancet* **1** 35 (Jan. 7) 1939.

86 Price, N. L. Gout Following Salyrgan Diuresis, *Lancet* **1** 22-23 (Jan. 7) 1939.

87 Short, J. J. Extreme Obesity Followed by Therapeutic Reduction of Two Hundred and Thirty-Nine Pounds, *J. A. M. A.* **111** 2196-2197 (Dec. 10) 1938.

pounds (180 Kg) to 156½ pounds (71 Kg) in twenty months. There was progressive improvement in health throughout the period and later. The diet was of the type proposed by Strang and Evans⁸⁸. Less than 600 calories were given, but supplementary vitamins were used in concentrated forms. Thyroid was used in the latter part of the period, the comment being made that thyroid is not well tolerated early because the metabolism in obesity actually is elevated. The elevation is in proportion to the increased surface area. In the case under discussion the production of heat was originally 56 per cent greater than what would be normal for a person of the patient's height and age if she were at normal weight. Such production of heat would be encountered in a person of normal weight with hyperthyroidism, the basal metabolic rate being +56 per cent. Many patients who are overweight exhibit symptoms also found with hyperthyroidism, namely, hypertension, tachycardia and diminished tolerance of dextrose. These symptoms may be directly related to the hypermetabolism.

An interesting discussion of the causes of obesity is contained in a paper by Greene,⁸⁹ in which observations were made on 350 patients. The high percentage of patients (67.5) who gave a history of diminished activity while they were gaining weight indicates, according to Greene, that in many cases "endogenous" obesity would be eliminated by a more detailed history. The story of increased intake of food, on the other hand, was obtained in only 3.2 per cent of the patients. The etiologic role of alterations in the thyroid, pituitary and ovarian secretions or of lesions in the hypothalamus was regarded as doubtful in all but very few cases. Diets low in calories were followed for an adequate time by 146 of the patients with satisfactory loss of weight, irrespective of whether the obesity was associated at the onset with a glandular disturbance or with chronic encephalitis.

XANTHOMATOSIS (LIPOID DISEASE)

Muller,⁹⁰ prompted by investigations of Harbitz into the deposition of xanthomatous substances in the body and aware of the frequent occurrence of angina pectoris in patients with cutaneous xanthoma tuberosum, was impressed with the familial character of the association. In two years he has collected 76 cases of xanthomatosis in only 17 families. In 68 of the patients signs of heart disease were

88 Strang and Evans, cited by Short⁸⁷

89 Greene, J. A. Clinical Study of the Etiology of Obesity, *Ann Int Med* 12: 1797-1803 (May) 1939

90 Muller, C. Angina Pectoris in Hereditary Xanthomatosis, *Arch Int Med* 64: 675-700 (Oct) 1939

found and in 59 of these angina pectoris. It seems to be Muller's opinion that xanthomatous deposits in the coronary arteries accounted for the angina, and that in 5 patients similar deposits on the valves of the heart were responsible for the valvular disorders. Most of the patients were in business or professions. Not one was of the "working classes," although much of Muller's practice is among persons of the working class.

This observation reported by Muller⁹⁰ impresses us as being of unusual importance. Interest in this disease has been limited, heretofore, largely to our colleagues in dermatology. It clearly is a condition which demands more general attention, as was emphasized in an earlier review.⁵⁰ The full-blown disease may involve many organs, the damage it does depends on the location of the accumulations of lipid. In a case reported by Layani and associates⁹¹ the extent of xanthomatous accumulations was remarkable. There were manifestations of (1) osteoarthritis (lipoid material with doubly refracting crystals was aspirated from joints), (2) biliary xanthoma with cirrhosis, (3) cutaneous xanthoma tuberosum, (4) vascular xanthoma with atherosclerosis and (5) hyperlipidemia. The values for blood lipoids were: total lipid, 4.880 Gm per hundred cubic centimeters, cholesterol, 1.340 Gm, cholesterol esters, 0.389 Gm, phospholipoid, 0.788 Gm.

This disease has been observed in a number of patients with diabetes mellitus, but its occurrence is by no means limited to such patients. In Layani's^{91a} case the values of the blood sugar during fasting were normal, and no other evidence of diabetes could be obtained. Layani and his associates^{91b} were inclined to the view that xanthomatosis depends on abnormal metabolic activity of the reticulo-endothelial cell. They ascribed, however, a dynamic component to this, considering that the abnormality involves something more than simple engorgement with lipid. They further suggested that an allergic influence may be involved, an opinion based on studies made by Schmidt.⁹² Schmidt, using sensitized animals for the experimental production of xanthomatosis, was able in a few days (two weeks) and with relatively small doses of cholesterol to obtain a degree of lipid infiltration of arteries which otherwise with larger doses of cholesterol would occur only after several months.

91 (a) Layani, F. Le rhumatisme chronique déformant xanthomateux, *Bull et mém Soc méd d hôp de Paris* **55** 343-355 (March 13) 1939. (b) Layani, F., Laudat, M., and Astruc, P. Sur un cas de maladie xanthomateuse, *ibid* **55** 355-367 (March 13) 1939.

92 Schmidt, H., cited by Layani, Laudat and Astruc⁹¹

II NUTRITION

BY DR BUTT

The greatest efforts in the field of nutrition during the past year have continued to be directed toward a further study of the chemical and physiologic properties of the vitamins and also toward clinical application of this knowledge. The magnitude of these efforts prohibits complete survey of each field of nutrition and thus limits the present review to those studies which are of most interest to clinicians.

Of the many interesting advances in the work on nutrition during the past year, the isolation and the synthesis of vitamins B₆ and K and the therapeutic application of vitamins B₆, K and riboflavin have been perhaps the most outstanding. Many other advances in the study of nutrition have afforded a new outlook on several diseases, and these will be considered.

VITAMIN A

Chemical and Physiologic Properties—In addition to vitamin A, vitamin A₂ has been reported, and during the past year most advances in the chemical investigation of vitamin A have concerned its partner, vitamin A₂. Biologically, vitamins A (A₁) and A₂ are the same, chemically, they are different.⁹³

In addition to the large amounts of vitamin A found in the liver oils of fish, Lovern and Morton⁹⁴ demonstrated the presence of large deposits in the tunica propria of the mucosa of the intestines of fish. Lease and his associates⁹⁵ reported that pure carotene, vitamin A and precursors of vitamin A are destroyed in rancid fats and that heating of fats to the temperatures which are used frequently in cooking destroys vitamin A to some extent, however, to what extent harmful rancidity develops during storage of food awaiting sale and consumption remains to be established.

In an excellent study dealing with the effects of various amounts of ingested liquid petrolatum on the absorption of carotene from the gastrointestinal tract in man, Curtis and Kline⁹⁶ showed that liquid petrolatum, given in amounts of 20 cc three times daily or twice daily before meals, or mixed with carotene, prevents absorption of carotene from ingested materials. Interesting enough, little, if any, effect on

93 Gillam, A. E. The Vitamin A₁ and A₂ Contents of Mammalian and Other Animal Livers, *Biochem J* **32** 1496-1500 (Sept.) 1938

94 Lovern, J. A., and Morton, R. A. The Distribution of Vitamins A and A₂ III, *Biochem J* **33** 330-337 (March) 1939

95 Lease, E. J., Lease, J. G., Weber, J., and Steenbock, H. Destruction of Vitamin A by Rancid Fats, *J. Nutrition* **16** 571-583 (Dec.) 1938

96 Curtis, A. C., and Kline, E. M. Influence of Liquid Petrolatum on Blood Content of Carotene in Human Beings, *Arch. Int. Med.* **63** 54-63 (Jan.) 1939

the concentration of carotene in the blood was demonstrated when liquid petrolatum was given in a single dose of 30 cc at bedtime. This study emphasized the importance of not giving liquid petrolatum at any time of day when it may be mixed with food in the gastrointestinal tract. Andersen⁹⁷ has reported similar studies.

Heifort⁹⁸ made an interesting study on the effect of vitamin A on pancreatic secretion. He reported that the secretion of the pancreas produced by ingestion of 80 units of secretin was no greater than that produced by ingestion of 20,000 units of vitamin A. The effect on secretion was noticed ten to fifteen minutes after ingestion and lasted forty to fifty minutes. Vitamin A administered intramuscularly produced the same results, but more slowly. Vitamin D had no such effect.

From several sources it appears that the distribution of vitamin A in the circulating blood and tissues is controlled in part by the nervous system. Direct excitation of the pneumogastric nerve causes discharge of vitamin A into the circulating blood,⁹⁹ and if animals are excited the content of vitamin A in the blood is greater than normal.¹⁰⁰

Effect of Deficiency on Nervous System—Deficiency of vitamin A apparently has a profound effect on the nervous system. Mellanby¹⁰¹ was able to produce deafness in young puppies by a diet deficient in vitamin A, and in the labyrinths of these animals degeneration of the cochlear neurons was the most obvious pathologic change. The work on rats by Irving and Richards¹⁰² indicates that degeneration of the medulla oblongata is one of the fundamental lesions of vitamin A deficiency.

Vitamin A Requirements of Man—The exact minimal vitamin A requirement of man is still unknown. Booher and his associates,¹⁰³

97 Andersen, O. Effect of Administration of Liquid Paraffin on the Absorption of Vitamin A in Human Subjects, *Hospitaltid (supp.)* **81** 29-41, 1938, abstracted, *Nutrition Abstr & Rev* **8** 750 (Jan) 1939.

98 Herfort, K. L'influence de la vitamine A sur la secretion externe du pancreas, *Acta med Scandinav* **96** 425-437, 1938.

99 Chevallier, A. Les facteurs de variation de la reserve hépatique en vitamine A (en particulier l'influence du système nerveux), *Nutrition* **7** 143-146, 1937.

100 Troitzki, G. V. Influence of the Nerves on the Vitamin A Content of Blood, *Bull biol méd exper U S S R* **5** 360-362, 1938, abstracted, *Nutrition Abstr & Rev* **8** 601 (Jan) 1939.

101 Mellanby, E. The Experimental Production of Deafness in Young Animals by Diet, *J Physiol* **94** 380-398 (Dec 14) 1938.

102 Irving, J. T., and Richards, M. B. Early Lesions of Vitamin A Deficiency, *J Physiol* **94** 307-321 (Dec 14) 1938.

103 Booher, L. E., Callison, E. C., and Hewston, E. M. An Experimental Determination of the Minimum Vitamin A Requirements of Normal Adults, *J Nutrition* **17** 317-331 (April) 1939.

in a study of 5 adult persons maintained on weighed diets adequate in all known food essentials except vitamin A, found that an average daily intake of vitamin A of not more than 103 international (U S P XI) units resulted in unmistakable signs of impaired adaptation to dark. The daily intake of vitamin A in the form of cod liver oil plus vitamin A supplied by the food which was necessary for the maintenance of normal adaptation to dark varied in the 5 persons studied between the limits of 25 and 55 international units per kilogram of body weight, the daily intake of carotene expressed in terms of international units of vitamin A varied in the 5 persons studied between the limits of 43 and 103 per kilogram of body weight. Unit for unit the carotene and cottonseed oil were about 50 to 60 per cent as effective in supporting normal adaptation to dark as vitamin A in the form of cod liver oil. McKenzie¹⁰⁴ also suggested that vitamin A exerts a more rapid and powerful action in causing disappearance of clinical signs of vitamin A deficiency than vegetable carotene, and Mead¹⁰⁵ and Underhill and Coward¹⁰⁶ found vitamin A to be twice as effective as betacarotene. No untoward effects from overdoses of vitamin A have been reported. Haig and his associates¹⁰⁷ have given as much as 500,000 units of vitamin A in a single dose without ill effect.

Effect on Specific Organs—(a) Eyes. The heated argument concerning the merits of adaptation to darkness as a test for vitamin A deficiency continues. This, as Josephs¹⁰⁸ well stated, may be due to the fact that we have not yet a method for determining deficient storage of vitamin A. Night blindness continued to be treated successfully with vitamin A by Vaillant and Gillis,¹⁰⁹ and others¹¹⁰ reemphasized that the measurements of adaptation to dark made under critically

104 McKenzie, A. An Examination of Vitamin A Deficiency Among African Natives by the Visual Dysadaptation Test, *Tr Roy Soc Trop Med & Hyg* **32** 717-728 (April) 1939.

105 Mead, T. H. Crystalline Esters of Vitamin A. I. Preparation and Properties, *Biochem J* **33** 589-594 (April) 1939.

106 Underhill, S. W. F., and Coward, K. H. Crystalline Esters of Vitamin A. II. Biological Potency, *Biochem J* **33** 594-600 (April) 1939.

107 Haig, C., Hecht, S., and Patek, A. J. Jr. Vitamin A and Rod-Cone Dark Adaptation in Cirrhosis of the Liver, *Science* **87** 534-536 (June 10) 1938.

108 Josephs, H. W. Studies in Vitamin A. Relation of Vitamin A and Carotene to Serum Lipids, *Bull Johns Hopkins Hosp* **65** 112-124 (July) 1939.

109 Vaillant, C., and Gillis, L. Night-Blindness Treated with Vitamin A. *Lancet* **1** 149-150 (Jan 21) 1939.

110 Hecht, S., and Mandelbaum, J. The Relation Between Vitamin A and Dark Adaptation, *J A M A* **112** 1910-1916 (May 13) 1939. Caussade, L., Neimann, N., Thomas, C., and Davidsohn. Recherches sur les tests oculaires d'hypovitaminose A chez les enfants d'âge scolaire, *Rev franç de pédiat* **14** 209-223, 1938, abstracted, *J A M A* **112** 676 (Feb 18) 1939.

standardized conditions can be used as an aid in diagnosis of avitaminosis A whether this is produced by lack of vitamin A in the diet or by functional disarrangements in the flow of vitamin A from the diet to the retina. New photometers and rapid visual tests for measuring the rate of adaptation to dark were described by Thomson, Griffith and associates¹¹¹ and Pett,¹¹² but others, among them Snelling,¹¹³ still contended that the results obtained by using the biophotometer are too inconsistent to allow one to regard it as a satisfactory instrument for measuring vitamin A nutrition.

It is extremely interesting that although pathologic adaptation to dark is noted often among patients with various diseases and in various states of undernutrition, yet results of attempts to produce pure vitamin A deficiency in man as measured by adaptation to dark have been for the most part controversial. Jung and Isaacs¹¹⁴ reported a study on 3 students who were placed on a diet deficient in vitamin A for one month. Adaptation to darkness was measured five times a week on the new Hecht adaptometer. Many fluctuations were noted during the month, but the normal control curves had the same drift. Doses of vitamin A up to 300,000 international units showed no effect on the measurements obtained by adaptometer. After fifty-four days on the deficient diet, the students continued to take vitamin A for one month at a larger dosage, but still no effect on the adaptation curves was observed. These authors concluded that it was unlikely that the measurement of adaptation to darkness provided a way of measuring the nutrition status of persons with respect to vitamin A.

Steffens and his associates¹¹⁵ reported that the thresholds of light intensity and the curves of adaptation to dark of 3 healthy adults were not affected significantly during their maintenance on a diet very low in vitamin A over periods of forty-four, one hundred and sixty and one hundred and ninety days, respectively. They reported that the persons studied were able to withstand considerable periods of deficiency in intake of vitamin A so far as concerned significant changes in retinal sensitivity. They did find, however, that microscopic examination of

111 Thomson, A. M., Griffith, H. D., Mutch, J. R., Lubbock, D. M., Owen, E. C., and Logaras, J. A Study of Diet in Relation to Health, Dark Adaptation as an Index of Adequate Vitamin A Intake, II. A New Photometer for Measuring Rate of Dark Adaptation, *Brit. J. Ophth.* **23** 461-478 (July) 1939.

112 Pett, L. B. A Rapid Visual Test for Vitamin A Deficiency, *Nature*, London **143** 23 (Jan. 7) 1939.

113 Snelling, C. E. The Biophotometer as a Test for Vitamin A Deficiency, *J. Pediatr.* **13** 506-509 (Oct.) 1938.

114 Jung, F. T., and Isaacs, B. L. Measurement of Vitamin A Deficiency in Man, *Proc. Inst. Med. Chicago* **12** 317-318 (March 15) 1939.

115 Steffens, L. F., Bair, H. L., and Sheard, C. Photometric Measurements on Visual Adaptation in Normal Adults on Diets Deficient in Vitamin A, *Proc. Staff Meet., Mayo Clin.* **14** 698-704 (Nov. 1) 1939.

the skin of the subject who was on a diet low in vitamin A for one hundred and ninety days revealed changes which generally occur in the late stages of A avitaminosis. The authors suggested that the normal values of sensitivity to light may be maintained over a considerable period of time, perhaps through the utilization of carotene in vitamin A previously deposited in the skin and fatty tissues, and that the minimal requirements of these substances for proper visual function may be much less than has been believed heretofore.

In contrast to these studies, Wald and Steven¹¹⁶ reported an excellent study on a subject whose diet was deficient in vitamin A, in which adaptation to darkness was measured. They found that each day of the deficient diet a constant fraction of what rhodopsin and vitamin A remained was lost. These investigators stated that vitamin A is the precursor of photopigments in addition to rhodopsin. They further demonstrated that

The first observable symptom of vitamin A-deficiency in man and other mammals is a rise of visual threshold known as night-blindness. This response is based at least in part on the direct participation of vitamin A in a retinal cycle with the photosensitive pigment of the rods, rhodopsin. As the level of vitamin A falls on a deficient diet, the concentrations of all components of the retinal cycle, including rhodopsin, decrease and the visual threshold reciprocally rises.

(b) Liver. It has been well established that the liver enacts a major role in the metabolism of vitamin A, but the exact manner in which this is accomplished is still unknown.

Thorbjarnarson and Drummond¹¹⁷ reported that the storage of vitamin A and its subsequent deposit in the liver of the rat are facilitated by the presence of fat in the diet and further that on giving choline to rats they noted a rapid depletion of the vitamin A reserve. This suggests that fat leaving the liver in response to choline takes some vitamin A with it. Lease and Steenbock¹¹⁸ were unable to confirm these observations.

As early as 1895 Hori¹¹⁹ had made the clinical observation that not infrequently night blindness and keratomalacia accompany disease of the liver, and forty years later Patek and Haig,¹²⁰ using modern methods

116 Wald, G., and Steven, D. An Experiment in Human Vitamin A-Deficiency, *Proc Nat Acad Sc* **25** 344-349 (July) 1939.

117 Thorbjarnarson, T., and Drummond, J. C. Conditions Influencing the Storage of Vitamin A in the Liver, *Biochem J* **32** 5-9 (Jan) 1938.

118 Lease, E. J., and Steenbock, H. Diet and Rate of Depletion of Hepatic Vitamin A, *J Nutrition* **17** 85-90 (Jan) 1939.

119 Hori, cited by Haig, Hecht and Patek¹⁰⁷.

120 Patek, A. J., Jr., and Haig, C. The Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, *J Clin Investigation* **18** 609-616 (Sept) 1939.

of measuring vitamin A deficiency, reported that 19 of 24 patients with alcoholic cirrhosis without jaundice had subnormal powers of adaptation to darkness, which improved on adequate administration of vitamins. Others have repeatedly demonstrated that the vitamin A in the liver¹²¹ and in the blood¹²² of patients with severe hepatic injury is nearly always markedly decreased, while in the urine it is increased¹²³.

Monceaux¹²⁴ suggested that since pathologic conditions of the liver result in incomplete transformation of carotene into vitamin A, fish liver oils should be given preference over carotene in the treatment of hepatic disease.

Of some interest is the observation¹²⁵ that injections of insulin lead to a diminution in the vitamin A content of the liver of the normal guinea pig, and less of the vitamin A fed is stored in the animal treated with insulin than in the untreated one. The conversion of carotene to vitamin A is said to be stimulated by insulin.

(c) *Epithelium*. A majority of investigators have failed to find any relation between the presence of stones in the urinary tract and a diet deficient in vitamin A, however, Ezickson and Feldman¹²⁶ have found a high percentage of persons with urinary lithiasis to have a deficiency of vitamin A. Renal and ureteral calculi were produced in 9 of 35 guinea pigs on a diet deficient in vitamin A. This deficiency apparently causes hyperplasia, then metaplasia and finally atrophy of the pelvic and ureteral mucosa. Large plaques of desquamated epithelium apparently acted as nuclei for the development of calculi. The stones produced in the animals were made of calcium carbonate, there was no evidence of

121 Moore, T. Vitamin A and Carotene. XIII. The Vitamin A Reserve of the Adult Human Being in Health and Disease, *Biochem J* **31** 155-164 (Jan) 1937.

122 Chevallier, A., Olmer, J., and Vague, J. Sur la valeur diagnostique et pronostique du taux de l'hémovitamine au cours des hépatites, *Bull et mem Soc med d hôp de Paris* **55** 928-932 (June 19) 1939. Lasch, F. Ueber den Vitamin A-Spiegel im Blute bei Leberkrankheiten, *Klin Wchnschr* **17** 1107-1108 (Aug 6) 1938.

123 Boller, R., Brunner, O., and Brodaty, E. Ueber die Ausscheidung von Vitamin A im Harn, *Wien Arch f inn Med* **31** 1-22, 1937.

124 Monceaux, R. H. Difficulté de transformation du carotène en facteur A au cours de nombreux états pathologiques, conséquences thérapeutiques, *J de pharm et chim* **28** 297-302, 1938, abstracted, *Nutrition Abstr & Rev* **8** 1062 (April) 1939.

125 Bauereisen, E. Untersuchungen über den Einfluss des Insulins auf die Carotin-Vitamin-A-Bestände der Leber, *Endokrinologie* **21** 247-252, 1939.

126 Ezickson, W. J., and Feldman, J. B. Further Studies of Vitamin A Deficiency in Individuals with Urinary Lithiasis. A Report of Further Clinical Studies and Investigations on Thirty-Six Patients, *Urol & Cutan Rev* **43** 302-304 (May) 1939.

infection¹²⁷ Although this work has not been accepted generally, it may, as stated in a recent article,¹²⁸ shed light on the causation of clinical urolithiasis

In several reports during the past year mention was made of the efficacy of vitamin A in the treatment of cutaneous diseases in man¹²⁹

Oppel¹³⁰ produced vascular disease in rats by multiple depletion of vitamin A The vascular disease apparently was due to the loss of elasticity, the formation of firm intramural plaques and the tortuosity of the vessels

Micro-ophthalmia has been noted in rats whose mothers were on a diet depleted in vitamin A,¹³¹ and Mutch and Richards¹³² observed keratoconus as a sequel to acute xerophthalmia in rats on a diet deficient in vitamin A Spies¹³³ reported that among 50 patients with long-continued dietary deprivation there developed photophobia, burning and itching of the eyes, and redness, which were corrected by the administration of vitamin A

(d) Thyroid A number of years ago Fasold and Heidemann¹³⁴ noted that the milk from goats, which is normally pure white, is yellowish after thyroidectomy, notwithstanding the fact that the diet is normal The latter color is due to failure to convert carotene into vitamin A A few years later it was suggested that the thyroid hormone was essential for the conversion of carotene and also for the storage of vitamin A in the liver Later carotenemia was observed in cases of hyperthyroidism,¹³⁵ and striking general improvement of patients with hyperthyroidism followed the administration of diets rich in vitamin A¹³⁶ It has been

127 Steiner, M, Zuger, B, and Kramer, B Production of Renal Calculi in Guinea Pigs by Feeding Them a Diet Deficient in Vitamin A, *Arch Path* **27** 104-114 (Jan) 1939

128 Renal Calculi in Vitamin A Deficiency, *Current Comment*, *J A M A* **112** 1595 (April 22) 1939

129 Rao, M V R Treatment of Phrynoderma by Vitamin-A Concentrate, *Indian M Gaz* **73** 461-463, 1938

130 Oppel, L Experimental Vascular Disease in Rats Produced by Multiple Depletions of Vitamin A, *Proc Soc Exper Biol & Med* **40** 449-450 (March) 1939

131 Browman, L G The Reproductive Performance of Albino Rats with Previous Vitamin A Depletion Histories, *Am J Physiol* **125** 335-338 (Feb) 1939

132 Mutch, J R, and Richards, M B Keratoconus Experimentally Produced in the Rat by Vitamin A Deficiency, *Brit J Ophth* **23** 381-387 (June) 1939

133 Spies, T D A Note on the Ocular Symptoms Occurring from Malnutrition in Human Beings, *Am J M Sc* **198** 40-41 (July) 1939

134 Fasold, H, and Heidemann, E R Ueber die Gelbfärbung der Milch thyreoprivier Ziegen, *Ztschr f d ges exper Med* **92** 53-56, 1933

135 Anderson, H H, and Soley, M H The Effects of Carotenemia on the Function of the Thyroid and the Liver, *Am J M Sc* **195** 313-318 (March) 1938

136 Soskin, S, and Mirsky, I A Medical Treatment of Hyperthyroidism with High Fat Diet, *J A M A* **110** 1337-1338 (April 23) 1938

reported repeatedly that the vitamin A in the blood of cretins is of decreased concentration or absent, whereas the value for carotene usually is high. From this, it may be assumed that the insufficiency of the thyroid prohibits the conversion of carotene into vitamin A. Histologic experiments on rats' livers revealed a definite antagonism between thyroxine and vitamin A in regard to glycogen content and the number of mitotic figures,¹³⁷ and the decline in concentration of serum lipase which follows the injection of thyroxine into rats can be prevented by the injection of vitamin A.¹³⁸ Wohl and Feldman¹³⁹ in a clinical study, using adaptation to dark, showed that hyperthyroidism depletes and destroys vitamin A reserve, as evidenced by pathologic adaptation to dark in 18 of 20 patients with thyrotoxicosis. Six patients with autonomic imbalance had normal adaptation to dark despite elevated basal metabolic rates, and 7 patients with hypothyroidism had markedly pathologic adaptation. The conclusion drawn from these studies is that the thyroid hormone is essential for the conversion and storage of vitamin A.

Vitamin A in Health and Disease—Clausen and McCoord¹⁴⁰ reported that carotene and xanthophyll may pass through the placenta to the fetus and that vitamin A itself may follow a similar course. They also found that normal infants and older persons could readily absorb carotene from the diet but that the rate of absorption is slower than the rate of absorption of vitamin A. They suggested that the lowered concentration of carotene found in infants during the first six months of life and in the winter months might be due to the low carotenoid content of the diet in early infancy and in the winter months. The mean concentration of vitamin A in the plasma of normal man apparently reaches a constant level soon after birth and then is not affected by season. The fall of concentration of vitamin A in the plasma noted during various infectious diseases is probably the result in part of a low intake of vitamin A and in part of fever. A few days after the temperature becomes normal the vitamin A content of the plasma may even rise considerably above the normal level.

137 Wegelin, C. On the Antagonism Between Thyroxine and Vitamin A, *West J Surg* **47** 147-154 (March) 1939.

138 Torok, G. Antagonism Between Thyroxine and Vitamins A and C, *Magyar orvosi arch* **39** 315-324, 1938.

139 Wohl, M. G., and Feldman, J. B. Vitamin A Deficiency in Disease of the Thyroid Gland. Its Detection by Dark Adaptation, *Endocrinology* **24** 389-396 (March) 1939.

140 Clausen, S. W., and McCoord, A. B. The Carotinoids and Vitamin A of the Blood, *J. Pediat* **13** 635-650 (Nov.) 1938.

Descriptions of the various methods used for measuring vitamin A need not be given here but can be found in several recent publications ¹⁴¹

Youmans,¹⁴² in a review of the literature on clinical disorders resulting from deficiency of vitamin A, pointed out that it is probable that the greatest incidence of vitamin A deficiency in practice occurs in patients in whom the deficiency is a complication rather than an independent disorder. Many articles continue to appear concerning the level of vitamin A in the blood and urine of patients with many diseases, but the exact significance of the findings cannot yet be interpreted properly. Getz and his associates ¹⁴³ found that in 53 per cent of tuberculous persons tested there was a deficiency of vitamin A and that this deficiency paralleled the severity of the tuberculosis. Kluth ¹⁴⁴ even found vitamin A of some value in treatment for gastritis and gastric and duodenal ulcers. A full discussion of the effect of vitamin A on various gastrointestinal disorders is given in a recent monograph by Lindqvist ¹⁴⁵

Abbott and his associates ¹⁴⁶ showed that the differential leukocyte count might be of value in diagnosing deficiency of vitamin A in man. In a study of the differential leukocyte counts of 157 persons whose diets and symptoms indicated vitamin A deficiency they noted rather characteristic changes in the blood picture.

VITAMIN B COMPLEX

The vitamin B complex continues to be the most baffling and most interesting field for research on vitamins. One of the most significant advances in this field during the past year was the demonstration by Jukes ¹⁴⁷ and by Woolley and his associates ¹⁴⁸ that the filtrate factor

141 Hedberg, J, and Lindqvist, T. Untersuchungen über das Vitamin A bei chronischen Nephritiden, *Acta med Scandinav (supp)* **90** 231-247, 1938. Lanzing, J. C. Determination of Vitamin A and Carotenoids in One to Two Cubic Centimeters of Blood, *Geneesk tijdschr v Nederl-Indie* **78** 3135-3144 (Dec 13) 1938.

142 Youmans, J. B. Newer Clinical Aspects of Vitamin Deficiency Diseases. Vitamin A Deficiency, *Am J Trop Med* **19** 229-242 (May) 1939.

143 Getz, H. R., Hildebrand, G. B., and Finn, M. Vitamin A Deficiency in Normal and Tuberculous Persons as Indicated by the Biophotometer, *J. A. M. A.* **112** 1308-1311 (April 8) 1939.

144 Kluth, H. J. Zur Wirkung von Vitamin A (Vogon) bei Magenerkrankungen, *Arch f Verdauungskr* **63** 177-190 (Sept) 1938, abstracted, *J. A. M. A.* **111** 2432 (Dec 24) 1938.

145 Lindqvist, T. Studien über das Vitamin A beim Menschen, *Acta med Scandinav (supp)* **97** 1-52, 1938.

146 Abbott, O. D., Ahmann, C. F., and Overstreet, M. R. Effect of Avitaminosis A on the Human Blood Picture, *Am J Physiol* **126** 254-260 (June) 1939.

147 Jukes, T. H. Pantothenic Acid and the Filtrate (Chick Anti-Dermatitis) Factor, *J Biol Chem* **129** 225-231 (July) 1939.

148 Woolley, D. W., Waisman, H. A., and Elvehjem, C. A. Nature and Partial Synthesis of the Chick Antidermatitis Factor, *J Am Chem Soc* **61** 977-978 (April) 1939.

(chick antidermatitis factor) is identical with pantothenic acid. Pantothenic acid is a substance which will greatly stimulate growth of yeast and which is of great importance in normal plant metabolism. Woolley and his associates found that pantothenic acid in addition to being a stimulant to growth of yeast is also a product of this growth. These authors pointed out that a similar situation exists with respect to thiamin (vitamin B₁), which may be both a stimulant to, and a product of, the growth of yeast.

Oleson and his associates¹⁴⁹ and Frost and Elvehjem¹⁵⁰ again reported that factor W is an essential factor for the rat, and Wyatt¹⁵¹ found some other new factors of the vitamin B complex which are necessary for the normal metabolism of the rat. Stokstad and Manning¹⁵² discovered a new growth factor, called factor U, which is present in large amounts in alfalfa and is necessary for normal growth of the chick. Bauernfeind and his co-workers¹⁵³ reported a new factor required for growth and reproduction of the domestic fowl.

In a study of 2 patients with pernicious anemia in relapse Heimle and Miller¹⁵⁴ observed that dried brewers' yeast apparently supplies an abundance of extrinsic factor and that pernicious anemia of certain patients may be corrected without specific therapy if an excess of this extrinsic factor is supplied. An excellent review of the whole problem of the relation of yeast and similar substances to the intrinsic and extrinsic factors in pernicious anemia and their effects in sprue and similar conditions was given by Rhoads¹⁵⁵ at a recent conference on therapy. Several authors¹⁵⁶ reported that the addition of yeast extract

149 Oleson, J. J., Bird, H. R., Elvehjem, C. A., and Hart, E. B. Additional Nutritional Factors Required by the Rat, *J. Biol. Chem.* **127** 23-42 (Jan.) 1939.

150 Frost, D. V., and Elvehjem, C. A. Factor W and Its Relation to the Vitamin B Complex, *J. Biol. Chem.* **128** 23-34 (April) 1939.

151 Wyatt, W. R. Evidence of Another Factor in the B Complex for Rats, *Proc. Soc. Exper. Biol. & Med.* **40** 281-283 (Feb.) 1939.

152 Stokstad, E. L. R., and Manning, P. D. V. Evidence of a New Growth Factor Required by Chicks, *J. Biol. Chem.* **125** 687-696 (Oct.) 1938.

153 Bauernfeind, J. C., Schumacher, A. E., Hodson, A. Z., Norris, L. C., and Heuser, G. F. A New Factor Required for Growth and Reproduction in the Domestic Fowl, *Proc. Soc. Exper. Biol. & Med.* **39** 108-111 (Oct.) 1938.

154 Heimle, R. W., and Miller, F. R. Yeast as an Extrinsic Factor in Relation to Pernicious Anemia, *J. Clin. Investigation* **18** 257-259 (May) 1939.

155 Vitamins. Vitamin B₂ Therapy, Conference on Therapy, *J. A. M. A.* **113** 297-302 (July 22) 1939.

156 Litchfield, H. R., Lichterman, J., Knoll, I., and Kurland, I. Effect of Yeast Extract (Vitamin B Complex) on Growth and Development of Premature Infants, *Am. J. Dis. Child.* **57** 546-553 (March) 1939. Summerfeldt, P., and Ross, J. R. Value of an Increased Supply of Vitamin B₁ and Iron in the Diet of Children. III, *ibid.* **56** 985-988 (Nov.) 1938.

to the diet of premature infants and young children is of considerable value in accelerating gain of weight and production of hemoglobin. No gastrointestinal disturbances have accompanied the administration of yeast extract in this group of cases.

Vitamin B₁ (Thiamin) —(a) Chemical and Physiologic Properties. The desirability of adopting synthetic vitamin B₁ hydrochloride as an international standard in place of the standard acid clay absorption product has become great. The National Institute for Medical Research¹⁵⁷ in Hampstead, London, procured an adequate amount of the synthetic material, contributed by four manufacturing firms. The potency of this material was compared with that of the acid clay absorption product in laboratories in Europe, America and Japan by various biologic and chemical methods. The results obtained showed a satisfactory degree of concordance, and the International Conference on Vitamin Standardisation unanimously agreed to the recommendation "that the specimen of pure synthetic vitamin B₁ hydrochloride which had been thus investigated should be defined as the potency of 3 microgrammes of the pure material." This recommendation of the International Conference on Vitamin Standardisation was adopted by the Permanent Commission on Biological Standardisation of the League of Nations Health Organisation. The previous international standard preparation, known as the standard absorption product of vitamin B₁, is now replaced, therefore, by the crystalline vitamin B₁ preparation.

Peters, Sinclair and associates¹⁵⁸ found little vitamin B₁ (free or bound) in the plasma of man, most of that which was found was bound inside or on the erythrocytes and particularly on the polymorphonuclear leukocytes. Tauber¹⁵⁹ made the comment that vitamin B₁ is present in mammalian tissues as a pyrophosphoric ester and is converted to the active coenzyme vitamin B₁ pyrophosphate.

During the past year there have been several studies concerning the excretion of ingested or injected thiamin chloride. Marrack and his co-worker¹⁶⁰ found that thiamin chloride injected intramuscularly into

157 Memorandum on the Second International Standard Vitamin B₁ Prepared by the Department of Biological Standards of the National Institute for Medical Research, Hampstead, London, N. W. 3, Bull. Health Organ., League of Nations **7** 874-876, 877-881 and 882-886, 1938, abstracted, Nutrition Abstr. & Rev. **8** 917 (April) 1939.

158 Peters, R. A., Sinclair, H. M., Wood, P., Ungley, C. C., and Goodhard, R. S. Discussion on the Clinical Aspects of the Vitamin-B Complex, Proc. Roy. Soc. Med. **32** 807-822 (May) 1939.

159 Tauber, H. The Intervention of Vitamin B₁ in Enzymic Reactions, J. Biol. Chem. **123** 499-506 (April) 1938.

160 Marrack, J. H., and Hollering, H. F. Excretion of Injected Aneurin (Vitamin B₁), Lancet **1** 325-326 (Feb. 11) 1939.

human beings was excreted rapidly during the first three hours after injection and that in the second three hours there was relatively little increase over the amount passed in the control periods. They assumed that a certain amount of thiamin is excreted by the kidneys before there is time for it to be stored in the body. They did not find any relation between the volume of urine and the amount of thiamin excreted. Within twenty-four hours after oral administration of 10 mg of thiamin chloride, Ritsert¹⁶¹ observed that 4 to 7 per cent of the dose was in the urine and 7 to 30 per cent in the feces. With parenteral administration of this dose, the figures were approximately in reverse. Schroder¹⁶² found that after intravenous injection of thiamin chloride the greater part was excreted within the first two hours. He found further that gastric and duodenal juice alone had no destructive effect on thiamin chloride but that hemin, if present, caused considerable, and bile some, destruction.

Richter and his associates,¹⁶³ in an interesting experiment on rats on a self-selected diet, found that animals on a diet deficient in vitamin B lost their appetite for carbohydrates and protein, whereas their appetite for fat increased. When yeast was made available to these rats, they consumed it eagerly, showing that vitamin-deficient animals reflect their needs in their appetites. The aversion of these animals toward protein is suggestive of some disturbance of protein utilization, and the authors suggested that some part of the vitamin B complex is needed for the intermediary metabolism of protein as well as of carbohydrate.

Burke and McIntyre¹⁶⁴ examined the insulin tolerance and the dextrose tolerance of albino rats being given normal diets, diets deficient in various combinations of the vitamin B factors and a normal diet supplemented by excess amounts of various vitamin B factors. When thiamin chloride was included in the diet of the rats, there was an increase in the hypoglycemic response to insulin. When a factor or factors present in "autoclaved, flavin-free rice polish concentrates" were included in the diet, the hypoglycemic effect of insulin was decreased. An excessive intake of the factor or factors in "autoclaved rice polish"

161 Ritsert, K. Ueber die Ausscheidung von peroral und parenteral zugefuhrtem Aneurin, *Klin Wchnschr* **17** 1397-1400 (Oct 1) 1938

162 Schroder, H. Untersuchungen uber den Stoffwechsel des B₁-Vitamins am Gesunden und Kranken, *Klin Wchnschr* **18** 148-150 (Feb 4) 1939

163 Richter, C. P., Holt, L. E., Jr., Barelare, B., Jr., and Hawkes, C. D. Changes in Fat, Carbohydrate and Protein Appetite in Vitamin B Deficiency, *Am J Physiol* **124** 596-602 (Dec) 1938

164 Burke, J. C., and McIntyre, A. R. The Effects of Vitamin B on Insulin Hypoglycemia and Sugar Tolerance, *J Pharmacol & Exper Therap* **64** 465-477 (Dec) 1938. McIntyre, A. R., and Burke, J. C. Vitamin B Fractions and Insulin Tolerance in the Albino Rat, *ibid* **65** 36-45 (Jan) 1939

was found to increase the sugar tolerance of these animals. These experiments were done carefully, were well controlled and deserve further study.

Villela¹⁶⁵ has been the first to report observation of thiamin chloride in the spinal fluid. Voit and Arnold¹⁶⁶ found no effect on gastric secretion after prolonged administration of thiamin chloride under normal and pathologic conditions.

(b) Vitamin B₁ Requirements of Man. It has been stated repeatedly that the American diet is deficient in thiamin chloride. Jolliffe¹⁶⁷ reported that the American diet now contains only a third of the vitamin B₁ present in the American and English dietary of a century ago. Whether or not this diet still provides a reasonable margin of safety in this essential nutrient is a question which can be answered only when man's approximate requirement of thiamin chloride is known and when the factors modifying this requirement have been established reasonably well. Some work had been carried out in Jolliffe's laboratory which suggested that small persons continuously excrete more thiamin in the urine than larger persons maintained on the same intake of calories and thiamin chloride. The author pointed out that a large fraction of our population, particularly persons who spend per capita \$2.00 per week for food, subsists on a dietary of borderline adequacy in vitamin B₁. He suggested that beriberi in the United States usually is classified under a variety of misleading diagnoses, such as alcoholic, diabetic or metabolic polyneuritis. Williams¹⁶⁸ also pointed out that the American diets in which white bread, maize meal and cereal products supply a large part of the calories are near the borderline for beriberi. He suggested that the human requirement for prevention of beriberi is about 1 mg of vitamin B₁ for each 3,700 nonfat calories. For diets containing large proportions of starch and small proportions of fat, such as prevail for the great part of the working population of the world, the minimal daily requirement per adult is apparently about 0.6 mg, or 200 international units, per day for an intake of 2,500 calories.

Baker and her associates¹⁶⁹ published the vitamin B₁ content of a number of foods in 1935 and again, during the past year, an important

165 Villela, G. G. Vitamin B₁ in Cerebrospinal Fluid, *Science* **89** 251 (March 17) 1939.

166 Voit, K., and Arnold, R. Untersuchungen über den Einfluss von B₁ auf die Säurewerte des Magens, *Klin. Wchnschr.* **18** 98-99 (Jan. 21) 1939.

167 Jolliffe, N. A Clinical Evaluation of the Adequacy of Vitamin B₁ in the American Diet, *Internat. Clin.* **4** 46-66 (Dec.) 1938.

168 Williams, R. R. Our Vitamin B₁ Supply in Relation to Human Needs, *Bull. New York Acad. Med.* **14** 641-646 (Oct.) 1938.

169 Baker, A. Z., and Wright, M. D. The Vitamin B₁ Content of Foods: Additional Values, *Biochem. J.* **32** 2156-2161 (Dec.) 1938.

article dealing with the vitamin B content of numerous other foods Mickelsen and his associates,¹⁷⁰ in a rather extensive study, showed that American consumption of meat is able to supply a considerable fraction of the daily requirements of vitamin B₁. This work demonstrated that meats are above the average in respect to their vitamin B₁ content and that they compare favorably with many foods which ordinarily are considered potent sources of this vitamin. It is assumed that the typical American diet contains about 7 per cent meat, according to calculations based on statistics of this sort, an average person secures over 200 international units of vitamin B₁ each day from his intake of meat alone. The daily human requirement for vitamin B₁ has been placed at 200 to 500 international units. Therefore, even though meats are used in the diet to the extent of only 7 per cent, they are capable of supplying a third of the human requirement for vitamin B₁. For instance, a pork chop, even when fried, may supply the total daily requirement of this vitamin.¹ These authors studied the stability of the vitamin under various types of household cooking, and their results indicate that there is slight destruction of the vitamin during frying, but during roasting, broiling or stewing the destruction approaches 50 per cent.

From experimentation on dogs, Arnold and Elvehjem¹⁷¹ suggested that if their results are applied to a man weighing 70 Kg on a 3,000 calory diet, he will require 187 to 250 international units of vitamin B₁ daily. Morgan and Haynes,¹⁷² in a study of the vitamin B₁ content of human milk as affected by ingestion of thiamin chloride, concluded that the vitamin B₁ content of human milk is controlled in the lower brackets by the vitamin B₁ content of the diet but that, as in cow's milk, a maximal level exists, above which the content of vitamin B cannot be raised even by massive doses of vitamin B₁. This work indicates that to feed expectant mothers thiamin chloride in an effort to be certain that the infant receives more of this vitamin is a somewhat useless procedure. This is in marked contrast to the result obtained from work on vitamin C, which will be mentioned subsequently.

170 Mickelsen, O, Waisman, H. A., and Elvehjem, C. A. Distribution of Vitamin B₁ (Thiamin) in Meat and Meat Products, *J. Nutrition* **17** 269-280 (March) 1939.

171 Arnold, A., and Elvehjem, C. A. Influence of the Composition of the Diet on the Thiamin Requirement of Dogs, *Am. J. Physiol.* **126** 289-298 (June) 1939.

172 Morgan, A. F., and Haynes, E. G. Vitamin B₁ Content of Human Milk as Affected by Ingestion of Thiamin Chloride, *J. Nutrition* **18** 105-114 (Aug. 10) 1939.

No serious untoward reactions resulting from the use of thiamin chloride have been reported. Steinberg,¹⁷³ however, during treatment of more than 300 patients for chronic arthritis with large doses of vitamin B₁, noted definite ill effects in about 1 per cent of the patients when 800 to 1,200 international units of vitamin B₁ was given by the oral route daily and 2,000 international units intravenously once a week. He reported 3 cases in which vitamin B₁ therapy apparently caused the development of herpes zoster, with intense burning pain and irritation of "peripheral nerve plates." The pain and irritation ceased when vitamin B₁ therapy was withdrawn.

(c) Methods of Measuring Vitamin B₁. During the past year much work has been directed toward perfecting a good test that would serve as a measurement of vitamin B₁.¹⁷⁴ Meiklejohn's test for vitamin B₁, using growth of fungus as the measurement, in the hands of Sinclair¹⁷⁵ was not found to be very satisfactory. Melnick and Field,¹⁷⁶ in a series of papers, described a quantitative test for thiamin chloride and also a chemical determination of vitamin B₁ which is specific for free thiamin but does not determine the quantity of vitamin in the phosphorylated form. Using the methods which they described, they found that dried yeast may contain as much as 75 per cent of its thiamin in the esterified form, while in polished rice and wheat germ the major portion exists as free vitamin B₁.

(d) Diagnosis and Treatment of Vitamin B₁ Deficiency Affecting Various Organs. 1. Central nervous system. There has been considerable controversy concerning the results of the use of thiamin chloride in the treatment for various neurologic disorders. Treatment

173 Steinberg, C. L. Untoward Effects Resulting from the Use of Large Doses of Vitamin B₁, *Am J Digest Dis* **5** 680-681 (Dec.) 1938.

174 Peters, R. A. The Catatorulin Test for Vitamin B₁, *Biochem J* **32** 2031-2036 (Nov.) 1938. Morell, T. Ein neuer biologischer Vitamin B₁-Test, *Deutsche med Wchnschr* **64** 1722-1723 (Nov 25) 1938. Liu, G. D. Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B₁-Deficient States. A Rapid, Specific and Sensitive Method for the Estimation of Blood Pyruvate, *Biochem J* **33** 249-254 (Feb.) 1939. Coward, K. H., and Morgan, B. G. E. The Biological Determination of Crystalline Vitamin B₁, *ibid* **33** 658-662 (May) 1939. Hennessy, D. J., and Cerecedo, L. R. The Determination of Free and Phosphorylated Thiamin by a Modified Thiochrome Assay, *J Am Chem Soc* **61** 179-183 (Jan.) 1939.

175 Sinclair, H. M. The Estimation of Vitamin B₁ in Blood, *Biochem J* **32** 2185-2199 (Dec.) 1938.

176 Melnick, D., and Field, H., Jr. Chemical Determination of Vitamin B₁. I. Reaction Between Thiamine in Pure Aqueous Solution and Diazotized *p*-Aminoacetophenone, *J Biol Chem* **127** 505-514 (Feb.) 1939, II. Method for Estimation of the Thiamine Content of Biological Materials with the Diazotized *p*-Aminoacetophenone Reagent, *ibid* **127** 515-530 (Feb.) 1939, III. Quantitative Enzymic Conversion of Cocarboxylase (Thiamin Pyrophosphate) to the Free Vitamin *ibid* **127** 531-540 (Feb.) 1939.

with thiamin chloride must be carried out on an adequately large and carefully controlled group of patients, and more results must be evaluated critically if more definite clinical facts are to be established. True polyneuritis can be produced not only by diets in which there is partial deficiency of the entire vitamin B complex but also by those which are adequate in thiamin but lacking the other factors in the complex. It seems fairly clear that vitamin B₁ deficiency is not the only etiologic factor in experimental nutritional polyneuritis of animals. Engel and Phillips¹⁷⁷ seldom observed neuropathologic changes in rats on a diet deficient in vitamin B₁, and they concluded that uncomplicated beriberi was not accompanied by degeneration of peripheral nerves. They found that administration of betacarotene or percomorph oil together with riboflavin removed all evidence of pathologic changes in the peripheral nerves of vitamin B₁ deficient chicks. Wintrobe and his associates¹⁷⁸ also found that in pigs symptoms referable to the nervous system were due apparently to deficiency of one or more other components of the vitamin B complex rather than to deficiency of thiamin chloride or of riboflavin alone. Jolliffe¹⁷⁹ brought this information together and attempted to ascertain the effect of vitamin B₁ and of the various factors modifying the response to thiamin chloride. For these studies they selected patients having mild polyneuritis which on the basis of history and of clinical characteristics was thought to be due to deficiency of vitamin B₁. He too found that diets containing a constant amount of vitamin B₁ but rich in the entire vitamin B complex led to greater improvement than did diets poor in vitamin B complex. The fraction of the complex responsible for this enhanced action of thiamin is not known. Evidence available indicates that it is not riboflavin or nicotinic acid and that it is not present in the highly concentrated fractions of liver extract effective in pernicious anemia. In the treatment of polyneuritis phosphorated vitamin B₁ is apparently no more or no less effective than thiamin chloride.

The value of thiamin chloride in treatment for neuritis of pregnancy has been studied extensively by Schultze¹⁸⁰. Among 750 pregnant

177 Engel, R. W., and Phillips, P. H. The Lack of Nerve Degeneration in Uncomplicated Vitamin B₁ Deficiency in the Chick and the Rat, *J. Nutrition* **16** 585-596 (Dec.) 1938

178 Wintrobe, M. M., Mitchell, D. M., and Kolb, L. C. Sensory Neuron Degeneration in Vitamin Deficiency. Degeneration of the Posterior Columns of the Spinal Cord, Peripheral Nerves and Dorsal Root Ganglion Cells in Young Pigs Fed a Diet Containing Thiamin (B₁) and Riboflavin but Otherwise Deficient in Vitamin B Complex, *J. Exper. Med.* **68** 207-220 (Aug.) 1938

179 Jolliffe, N. The Diagnosis, Treatment and Prevention of Vitamin B₁ Deficiency, *Bull. New York Acad. Med.* **15** 469-478 (July) 1939

180 Schultze, K. W. Schwangerschaftsneuritis und B₁-Vitamin, *Zentralbl. f. Gynak.* **62** 2533-2538 (Nov. 12) 1938, abstracted, *Nutrition Abstr. & Rev.* **8** 1067 (April) 1939

women examined in one year, 60 had neuritis of pregnancy. The first symptoms were painful twinges in the arms or legs, definite cramp, muscular weakness and fatigue often followed, clumsiness of movement also was commonly noticed. Severe generalized polyneuritis was seen as a rule only in association with hyperemesis gravidarum. Of the 60 patients treated by combined injection and oral administration of thiamin chloride, 37 had good results, 16 had fair results and 7 showed the condition unchanged. These results are fairly good, but it must be remembered that 7 per cent of women who have neuritis during pregnancy will have a spontaneous cure after delivery. Hildebrandt and Otto¹⁸¹ suggested that in the presence of severe paralytic symptoms during pregnancy the interruption of the pregnancy should be postponed until thorough treatment with thiamin chloride has been tried. Stahler¹⁸² attempted to show that the requirement of vitamin B₁ for the patient with polyneuritis of pregnancy is greater than normal. He observed that the amount of vitamin B₁ excreted in the urine after daily intramuscular injection of 10 mg of the vitamin was less in pregnant than in nonpregnant women and that in the presence of polyneuritis of pregnancy the amount excreted was still smaller. Thus the amount needed to produce saturation was much greater for the patient with polyneuritis.

It has been claimed that thiamin chloride is of some value in the treatment of diabetic neuritis. Needles,¹⁸³ however, found that in 3 cases of neuritis associated with diabetes the diet was adequate in thiamin chloride. Naide¹⁸⁴ reported that thiamin chloride is of some value in the treatment of pain of ischemic origin. Ten patients with ischemic neuritis were treated with doses of 100 mg of thiamin chloride twice a week for one month, 7 of these patients obtained complete relief, 2 reported partial relief and 1 failed to obtain relief. Doses of 20 to 100 mg of thiamin chloride were given thereafter once or twice a week as maintenance doses. Gangrene, ulcers and objective neurologic features were not improved by thiamin chloride. In 2 cases of intermittent claudication the results of thiamin chloride therapy were equi-

181 Hildebrandt, A., and Otto, H. Ueber Schwangerschaftspolyneuritis und ihre Beziehung zum Vitamin B₁, *München med Wchnschr* **85** 1619-1622 (Oct 21) 1938

182 Stahler, F. Untersuchungen über den Vitamin B₁-Stoffwechsel gesunder und polyneuritiskrankter Schwangerer und Wöchnerinnen, *Deutsche med Wchnschr* **64** 1137-1140 (Aug 5) 1938

183 Needles, W. Vitamin Studies in Cases of Diabetic Neuritis, *Arch Neurol & Psychiat* **41** 1222-1228 (June) 1939

184 Naide, M. The Use of Vitamin B₁ in Rest Pain of Ischemic Origin, *Am J M Sc* **197** 766-773 (June) 1939

vocal Naide suggested treatment with thiamin chloride for the pain arising from peripheral vascular disease. Keil¹⁸⁵ suggested the use of thiamin chloride in the treatment of nerve leprosy, and Chase¹⁸⁶ found thiamin chloride of no value in the treatment of schizophrenia.

2 Heart Dustin and his associates¹⁸⁷ reported on the electrocardiographic changes in several cases in which there was a history of unbalanced diet and clinical evidence of vitamin B₁ deficiency. Features commonly seen were an increase in the electrical systole, a rapid rate, a tendency to low voltage and in most cases a flattening of the T wave in leads, I, II and III. During treatment slowing of the rate, increase in voltage and varying changes in the ventricular complexes occurred in all cases. Kalaja and his associate¹⁸⁸ attempted to elucidate the cause of the cardiac disturbances which occur in vitamin B₁ deficiency by injecting into rabbits, pigeons and rats such metabolic products as are known or might be expected to occur in the organism in increased quantities during deficiency of vitamin B₁. Lactic, pyruvic and other acids were found to have distinct retarding effects on the cardiac rate of rabbits and pigeons, but in rats these acids, subcutaneously injected, caused a vagus-independent sinus bradycardia of the same type as that held characteristic of vitamin B₁ deficiency. It is difficult to attribute such minor cardiac changes to deficiency of vitamin B₁ alone. It seems that with such general disability as patients and animals exhibit in vitamin B₁ deficiency various changes in the body structure in general might be expected.

3 Thyroid Several workers, among whom is Drill,¹⁸⁹ have shown that hyperthyroid rats which had lost weight and which still received thyroid regained their loss of weight when both vitamin B₁ and the B complex were added to the diet. If vitamin B₁ alone was fed, the animals stopped losing weight, but did not gain until yeast or a yeast concentrate was fed. Such experimental observations have suggested the use of these materials in the preoperative preparation of patients

185 Keil, E. Ist Nervenlepra atologisch einheitlich? Zur Vitamin B₁-Behandlung der Nervenlepra, Arch f Schiffs- u Tropen-Hyg **42** 1-13 (Jan) 1938

186 Chase, L. H. Effects of Vitamin B₁ in Schizophrenia, Am J Psychiat **95** 1035-1038 (March) 1939

187 Dustin, C. C., Weyler, H., and Roberts, C. P. Electrocardiographic Changes in Vitamin B₁ Deficiency, New England J Med **220** 15-21 (Jan 5) 1939

188 Kalaja, L., and Narvanen, R. A Study of the Factors Which Cause the Heart Disturbances in Vitamin-B Deficiencies, Skandinav Arch f Physiol **79** 303-312 (Oct) 1938

189 Drill, V. A. Effect of Vitamin B₁ and Vitamin B₂ Complex on the Loss of Weight Produced in Rats by Experimental Hyperthyroidism, Proc Soc Exper Biol & Med **39** 313-316 (Nov) 1938

with hyperthyroidism Frazier and Ravdin¹⁹⁰ reported beneficial effects following administration of thiamin chloride to such patients They gave vitamin B₁ to 50 of their patients, while a control group of patients received the routine preoperative treatment without the vitamin To the first group 10 mg of crystalline thiamin chloride was given in solution hypodermically every other day and 10 Gm of brewers' yeast daily by mouth The group of 50 patients given the vitamin supplements showed a greater reduction in pulse rate and a greater gain in weight and appetite and required a shorter period for adequate preparation than did the 28 patients receiving no vitamin supplements The most marked benefit occurred in the nontoxic patients The authors suggested that although vitamin B₁ probably has no direct antithyrogenic action in man, adequate amounts of this vitamin should be an important aid in treating severe clinical hyperthyroidism

4 Liver Ochoa and Peters¹⁹¹ showed experimentally that administration of thiamin chloride to animals leads to immediate accumulation of both thiamin chloride and its pyrophosphoric ester in the liver, and they assumed that the liver is concerned intimately with the metabolism of vitamin B₁ It was found that liver converted vitamin B₁ into cocarboxylase in vitro Other evidence presented in this review indicates that the liver is concerned intimately in the metabolism of almost all of the vitamins, and clinical evidence available suggests that a conservative use of vitamin supplements in the treatment of hepatic disease is of considerable value

Riboflavin—The importance of riboflavin in the oxidation enzymes is fairly well established Warburg and Christian¹⁹² reported that five oxidation enzymes containing riboflavin have been described Riboflavin is not distributed widely in nature, but Darby and Day¹⁹³ reported that fresh liver, whether from beef, veal or pork, is equivalent in riboflavin content to many samples of dried yeast and on the basis of dried weight is apparently the richest known food source of riboflavin

In the experimental animal a deficiency of riboflavin produces several unusual effects In the hen such deprivation causes increase in the fat

190 Frazier, W D, and Ravdin, I S The Use of Vitamin B₁ in the Preoperative Preparation of the Hyperthyroid Patient, *Surgery* **4** 680-686 (Nov) 1938

191 Ochoa, S, and Peters, R A Vitamin B₁ and Cocarboxylase in Animal Tissues, *Biochem J* **32** 1501-1515 (Sept) 1938, abstracted, *Nutrition Abstr & Rev* **8** 621 (Jan) 1939, Quantitative Measurement of Vitamin B₁ and Its Phosphoric Esters and Their Synthesis in Animal Tissues, *Nature, London* **142** 356, 1938

192 Warburg, O, and Christian, W Bemerkung uber gelbe Fermente, *Biochem Ztschr* **298** 368-377, 1938, abstracted, *Nutrition Abstr & Rev* **8** 931-932 (April) 1939

193 Darby, W J, and Day, P L The Riboflavin Content of Meats, *J Nutrition* **16** 209-218 (Sept) 1938

content of the liver,¹⁹⁴ and in rats it produces cataracts¹⁹⁵ Riboflavin also has been shown to be necessary for normal growth and physical well-being in the pig¹⁹⁶

Bessey and Wolbach¹⁹⁷ reported that vascularization of the cornea of the rat in the absence of antecedent pathologic changes is probably a specific and most reliable criterion of riboflavin deficiency Whether or not this test can be used as a biologic measure of riboflavin remains to be seen

Since it was reported that riboflavin is important in the oxidation enzyme system, it has been felt that this material is necessary in normal human nutrition Proof of this, however, has not been available until the past year In 1938 Sebrell¹⁹⁸ reported that dogs on a blacktongue-producing diet to which nicotinic acid had been added died unless riboflavin was given, and Street and Cowgill¹⁹⁹ reported similar observations Later Sebrell and Butler²⁰⁰ reported that, of a group of 18 women who were maintained on a diet containing cornmeal, cowpeas, lard, casein, flour, white bread, calcium carbonate, tomato juice, cod liver oil, syrup, syrup of iron iodide, ascorbic acid and vitamin B₁, 10 had, within from ninety-four to one hundred and thirty days, lesions on the lips, to which the name "cheilosis" was given The lesions on the lips began as a pallor of the mucosa at the angles of the mouth without involvement of the buccal mucosa Maceration and superficial transverse fissures appeared within a few days These lesions resembled closely those described as perlèche Four of the 10 women with cheilosis were treated with daily doses of 1 or 2 mg of synthetic crystalline riboflavin for from three to ten days, after which the dose was changed to 0.25 mg per kilogram of body weight All lesions disappeared com-

194 Lepkovsky, S, Taylor, L W, Judkes, T H, and Almquist, H C The Effect of Riboflavin and the Filtrate Factor on Egg Production and Hatchability, *Hilgardia* **11** 559-591, 1938

195 Day, P L, Darby, W J, and Cosgrove, K W The Arrest of Nutritional Cataract by the Use of Riboflavin, *J Nutrition* **15** 83-90 (Jan) 1938

196 Hughes, E H The Role of Riboflavin and Other Factors of the Vitamin-B Complex in the Nutrition of the Pig, *J Nutrition* **17** 527-533 (June) 1939

197 Bessey, O A, and Wolbach, S B Vascularization of the Cornea of the Rat in Riboflavin Deficiency, with a Note on Corneal Vascularization in Vitamin A Deficiency, *J Exper Med* **69** 1-12 (Jan) 1939

198 Sebrell, W H Vitamins in Relation to the Prevention and Treatment of Pellagra, *J A M A* **110** 1665-1672 (May 14) 1938

199 Street, H R, and Cowgill, G R Acute Riboflavin Deficiency in the Dog, *Am J Physiol* **125** 323-334 (Feb) 1939

200 Sebrell, W H, and Butler, R E Riboflavin Deficiency in Man A Preliminary Note, *Pub Health Rep* **53** 2282-2284 (Dec 30) 1938 Riboflavin Deficiency in Man, Current Comment, *J A M A* **112** 1261 (April 1) 1939

pletely after five, six, twenty and forty-seven days of treatment, respectively. Another series of 4 women with cheilosis were treated with daily doses of 100 mg of nicotinic acid for five days. At the end of five days the lesions in all 4 women were definitely worse, and treatment with riboflavin was started. The lesions of 3 of the women disappeared completely after twelve, thirteen and twenty-four days of treatment, but those of the fourth were so much more serious that after forty-nine days the daily dose of riboflavin was increased to 0.05 mg per kilogram of body weight. Thereafter symptoms receded rapidly. One woman was treated with 100 mg of nicotinic acid for forty-three days. At the end of that time, the lesion still being present, riboflavin was added to the diet. Complete healing occurred within ten days. In the remaining instance typical cutaneous lesions of pellagra developed thirty-six days after the study was begun and were allowed to progress for four days. After use of 30 mg of nicotinic acid daily for thirty days, these lesions were healed completely, although the cheilosis remained twenty-one days after the cutaneous lesions of pellagra had healed and was not controlled until after riboflavin had been administered. Although these observations are preliminary, they are intensely interesting, they indicate that a specific clinical syndrome can be produced experimentally and that in human beings the early development of cheilosis can be alleviated by the administration of small doses of riboflavin. The authors suggested that the term "ariboflavinosis" be added to the nomenclature of diseases due to vitamin deficiency to designate this syndrome.

Landor²⁰¹ described cases of angular stomatitis, sore tongue and eczema of the scrotum in which administration of nicotinic acid did not effect cure but yeast did. In view of Sebrell's report one might deduce that deficiency of riboflavin may be at fault in such cases.

Nicotinic Acid —(a) Chemical and Physiologic Properties. Nicotinic acid is a member of the vitamin B complex which also is related intimately to the enzyme system. Thiamin is related to carboxylase, riboflavin is a component of flavoproteins and probably of other enzymes, and nicotinic acid is a component of both cozymase I and cozymase II, which are coenzymes for a large number of oxidation mechanisms.

Because of this close relationship between nicotinic acid and respiratory enzymes, Kohn,²⁰² in an excellent study, attempted to determine whether or not the coenzyme-like substance in the blood was altered in cases of deficiency of nicotinic acid. Theoretically, the coenzyme

201 Landor, J. V. Deficiency of Vitamin B₂, *Lancet* **1** 1368-1370 (June 17) 1939.

202 Kohn, H. I. The Concentration of Coenzyme-Like Substance in Blood Following the Administration of Nicotinic Acid to Normal Individuals and Pellagrins, *Biochem J* **32** 2075-2083 (Dec.) 1938.

level of the body of the patient with pellagra is reduced, this leads directly to reduced capacity for oxidation and reduction. Variations in the amount of dietary nicotinic acid should lead directly to variation in the amount of coenzyme. By measuring the coenzyme content of the blood of normal persons and those with pellagra, Kohn found that nicotinic acid increases cozymase I in normal persons and in pellagrins. Vilter and his associates²⁰³ reported similar results.

It has been shown that nicotinic acid will cure pellagra in monkeys,²⁰⁴ but it is apparently not essential for good health in rats²⁰⁵ or lambs²⁰⁶. Crandall and his associates²⁰⁷ suggested that nicotinic acid is essential for normal gastrointestinal motility. These workers used it in treating 65 patients for functional digestive disorders over a period of from two months to two years, and 60 per cent showed a good response. Thiamin chloride and riboflavin had no effect.

In the literature on the treatment of pellagra repeated emphasis is placed on the importance of giving in addition to nicotinic acid other members of the vitamin B complex. Helmer and Fouts,²⁰⁸ in a study on rats, demonstrated that a diet producing blacktongue produces many other deficiencies which are corrected only by the administration of the vitamin B₂ complex. Spies and his associates²⁰⁹ also emphasized this important factor.

Vilter and his associates²¹⁰ described a method for measuring nicotinic acid in the urine and reported that persons on a normal diversified

203 Vilter, R. W., Vilter, S. P., and Spies, T. D. Relationship Between Nicotinic Acid and a Codehydrogenase (Cozymase) in Blood of Pellagrins and Normal Persons, *J. A. M. A.* **112** 420-422 (Feb. 4) 1939, Determination of the Codehydrogenases I and II (Cozymase) in the Blood of Diabetics in Severe Acidosis, *Am. J. M. Sc.* **197** 322-326 (March) 1939.

204 Harris, L. J. The Vitamin B₂ Complex. Further Notes on "Monkey Pellagra" and Its Cure with Nicotinic Acid, *Biochem. J.* **32** 1479-1481 (Sept.) 1938.

205 Birch, T. W. The Requirements of the Dog and the Rat for Nicotinic Acid, *J. Nutrition* **17** 281-292 (March) 1939.

206 Pearson, P. B., Schmidt, H., and Mackey, A. K. Effect of a Pellagra-Producing Diet on Herbivora, *Proc. Soc. Exper. Biol. & Med.* **40** 423-425 (March) 1939.

207 Crandall, L. A., Jr., Chesley, F. F., Hansen, D., and Dunbar, J. The Relationship of the P-P Factor to Gastrointestinal Motility, *Proc. Soc. Exper. Biol. & Med.* **41** 472-474 (June) 1939.

208 Helmer, O. M., and Fouts, P. J. Multiple Nature of the Deficiency of Blacktongue-Producing Diets as Shown by Studies on Rats, *J. Nutrition* **16** 271-277 (Sept.) 1938.

209 Spies, T. D., Bean, W. B., and Ashe, W. F. Recent Advances in the Treatment of Pellagra and Associated Deficiencies, *Ann. Int. Med.* **12** 1830-1844 (May) 1939.

210 Vilter, S. P., Spies, T. D., and Mathews, A. P. A Method for Determination of Nicotinic Acid, Nicotinamide, and Possibly Other Pyridine-Like Substances in Human Urine, *J. Biol. Chem.* **125** 85-98 (Sept.) 1938.

diet excrete approximately 20 to 50 mg of nicotinic acid or its conjugates daily. Pellagrins in relapse or normal persons on a diet such as pellagrins usually consume excrete little if any color-producing derivatives of nicotinic acid.

(b) Use of Nicotinic Acid in Pellagra. According to Spies and Cooper,²¹¹ three groups of pellagrins are recognized: (1) "endemic" pellagrins, who through poverty or idiosyncrasy have subsisted for long periods on deficient diets, (2) pellagrins who have suffered from an organic disease which has caused them to subsist on an inadequate diet or has rendered them incapable of utilizing the food taken, and (3) pellagrins who suffer from chronic alcoholism and who fail in consequence to consume adequate food. The symptoms of the disease, however, and the treatment recommended are the same no matter to which group the patient belongs. The important points of the treatment of pellagrins with nicotinic acid have been covered fully in several papers.²¹² It is pointed out that an occasional patient may have considerable flushing of the face and neck and burning and tingling of the skin following the ingestion or injection of comparatively small doses of nicotinic acid. No other serious untoward reactions have been reported. Doses, however, of 1 Gm a day were found to produce definite toxic symptoms. Ruffin and Smith^{212b} obtained good results in the treatment of pellagrins from daily doses of 1.5 mg of nicotinic acid per kilogram of body weight by mouth. This quantity could be given either parenterally or in solution by mouth. It was observed that when nicotinic acid was given in tablets or in capsules much less satisfactory results were noted than when it was administered parenterally or in solution by mouth. Lewis²¹³ reported that a patient with pellagra was treated successfully with intravenous injections of sodium thiosulfate, given twice weekly. Cure of this patient was produced without any change in the diet.

It is well known that extracts of the livers of patients dying from pernicious anemia do not contain the hemopoietic factor which is usually

211 Spies, T. D., and Cooper, C. Vitamin Deficiency. The Diagnosis of Pellagra, *Internat Clin* **4** 1-11, 1938.

212 (a) Sydenstricker, V. P., Schmidt, H. L., Jr., Fulton, M. C., Neio, J. S., and Geeslin, L. E. Treatment of Pellagra with Nicotinic Acid. Observations in Forty-Five Cases, *South M J* **31** 1155-1163, 1938. (b) Ruffin, J. M., and Smith, D. T. Treatment of Pellagra with Special Reference to the Use of Nicotinic Acid, *ibid* **32** 40-47 (Jan.) 1939. (c) Musick, V. H. A Report of Ten Cases of Pellagra Treated with Nicotinic Acid, *Am J Digest Dis* **5** 807-809 (Feb.) 1939. (d) Blankenhorn, M. A., and Spies, T. D. Treatment of Pellagra with Nicotinic Acid, *Tr A Am Physicians* **53** 115-119, 1938.

213 Lewis, D. R. A Case of Pellagra Successfully Treated with Intravenous Injections of Sodium Thiosulphate, *Indian M Gaz* **73** 616 (Oct.) 1938, abstracted, *Nutrition Abstr & Rev* **8** 1075 (April) 1939.

found in the liver of the normal person Sydenstricker and his associates²¹⁴ found that an extract of the liver of a patient dying of pellagra was rich in the hemopoietic factor but lacking in the pellagra-curing substance present in commercial liver extract

Spies and his associates²¹⁵ were among the first to report that a porphyrin-like substance was present in the urine of patients with pellagra and that the excretion of this material was somewhat related to the severity of the symptoms Watson²¹⁶ found that the test devised by Beckh, Ellinger and Spies did not measure the porphyrin excreted in 4 cases of alcoholic pellagra A few authors have criticized this test as not being specific for porphyrin and as a quantitative test that is unsatisfactory in the presence of certain substances, particularly derivatives of urobilinogen, which give rise to disturbing colors In 3 of 4 specimens of urine from patients with pellagra which were examined, Watson noted red pigment, and one of them after the addition of the toluene preservative turned pinkish red From one of these urines Watson obtained a pigment in crystalline form of the nature of a derivative of indigo Further observations on this red pigment in the urine of pellagrins were reported by Watson,²¹⁷ who found the pigment to be uroiosein and, in contrast to claims of Spies and other workers, of no value in recognizing early states of pellagra

Nicotinic acid also has been reported useful in treatment for acrodynia,²¹⁸ and Bing and Broager²¹⁹ found that administration of nicotinic acid to 2 patients with idiopathic steatorrhea resulted in a marked decrease in diarrhea Nicotinic acid particularly reduced the water content of the feces, but no other symptoms of sprue were affected in the same distinct manner as the diarrhea When the administration of nicotinic acid was discontinued, diarrhea began again

Vitamin B₆.—During the past year the structure of vitamin B₆ has been established independently by laboratories abroad²²⁰ and in this

214 Sydenstricker, V P, Schmidt, H L, Jr, Geeslin, L E, and Weaver, J W The Liver in Pellagra, *Am J M Sc* **197** 755-762 (June) 1939

215 Beckh, W, Ellinger, P, and Spies, T D Porphyrinuria in Pellagra, *Quart J Med* **6** 305-319 (July) 1937

216 Watson, C J The Urinary Pigments in Four Cases of Alcoholic Pellagra, *Proc Soc Exper Biol & Med* **39** 514-518 (Dec) 1938

217 Watson, C J Further Observations on the Red Pigments of Pellagra Urines, *Proc Soc Exper Biol & Med* **41** 591-595 (June) 1939

218 Tisdall, F F, Drake, T G H, and Brown, A Nicotinic Acid in the Treatment of Acrodynia, *J Pediat* **13** 891-893 (Dec) 1938

219 Bing, J, and Broager, B Investigations on Effects of Administration of Nicotinic Acid in Two Patients with Idiopathic Steatorrhea (Sprue), *Ugesk f læger* **100** 1127 (Oct 6) 1938

220 Kuhn, R, Wendt, G, and Westphal, K Diet Konstitution des Adermins, *Ber d deutsch chem Gesellsch* **72** 310-311 (Feb 8) 1939

country The American investigators ²²¹ also reported complete synthesis of the vitamin as conclusive support for the proposed structure The structure of vitamin B₆ has proved to be 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine Wiard ²²² gave credit to the Japanese worker Ohdake for being the first to crystallize vitamin B₆ This worker several years previously had given approximately the same empiric formula as that now given by the other workers just mentioned

Rats on a diet deficient in vitamin B₆ show atrophy of the thymus, according to Dimick and Schreffler,²²³ and fatty livers, which the administration of choline does not wholly correct, according to Halliday ²²⁴ In young puppies a deficiency of this vitamin produced anemia ²²⁵ Birch ²²⁶ even suggested that this vitamin is in some way connected with the utilization of fatty acids, Robbins and Schmidt ²²⁷ found vitamin B₆ important for the growth of plants and suggested that it might prove to be as generally significant for living organisms as thiamin

The only clinical application which has been attempted with vitamin B₆ has been reported by Spies and his associates ²²⁸ These authors noted that 4 patients who had been treated successfully for pellagra and beriberi but who remained on their deficient diet complained of extreme nervousness, insomnia, irritability, abdominal pain, weakness and difficulty in walking Within four hours after the intravenous administration of

221 Harris, S A , Stiller, E T , and Folkers, K Structure of Vitamin B₆ II J Am Chem Soc **61** 1242-1244 (May) 1939 Harris, S A , and Folkers, K Synthetic Vitamin B₆, Science **89** 347 (April 14) 1939, Synthesis of Vitamin B₆, J Am Chem Soc **61** 1245-1247 (May) 1939 Stiller, E T , Keresztesy, J C , and Stevens, J R The Structure of Vitamin B₆ I, *ibid* **61** 1237 (May) 1937

222 Wiard, P W Crystalline Vitamin B₆ (Adermin), Nature, London **142** 1158 (Dec 31) 1938

223 Dimick, M K , and Schreffler, C B The Factor I (Vitamin B₆) Requirement of the Rat, J Nutrition **17** 23-29 (Jan) 1939

224 Halliday, N Fatty Livers in Vitamin B₆ Deficient Rats, J Nutrition **16** 285-290 (Sept) 1938

225 Fouts, P J , Helmer, O M , Lepkovsky, S , and Jukes, T H Production of Microcytic Hypochromic Anemia in Puppies on Synthetic Diet Deficient in Rat Anti-Dermatitis Factor (Vitamin B₆), J Nutrition **16** 197-207 (Aug) 1938

226 Birch, T W The Relation Between Vitamin B₆ and the Unsaturated Fatty Acid Factor, J Biol Chem **124** 775-793 (Aug) 1938, J Clin Investigation **17** 528, 1938

227 Robbins, W J , and Schmidt, M B Vitamin B₆, a Growth Substance for Excised Tomato Roots, Proc Nat Acad Sc **25** 1-3 (Jan) 1939

228 Spies, T D , Bean, W B , and Ashe, W F A Note on the Use of Vitamin B₆ in Human Nutrition, J A M A **112** 2414-2415 (June 10) 1939

50 mg of pure synthetic vitamin B₆ in sterile physiologic solution of sodium chloride, all patients experienced dramatic relief of these symptoms, and within twenty-four hours all symptoms had disappeared. These observations indicated to the authors that vitamin B₆ was important in human nutrition and supported the hypothesis already mentioned that deficiency diseases are often multiple in nature.

VITAMIN C

Chemical and Physiologic Properties—In a recent report²²⁹ by the Council on Pharmacy and Chemistry of the American Medical Association the use of the term "cevitamic acid" as the official term for use in the book "New and Nonofficial Remedies" was abandoned in favor of "ascorbic acid," with the understanding that the term "cevitamic acid" was to be included as a synonym to follow "ascorbic acid" and with the distinct understanding that this action is not to be a precedent so far as therapeutically suggestive names are concerned.

It seems fairly well established that vitamin C is connected intimately with the complementary activity of the serum²³⁰ and that it plays some part in the process of agglutination²³¹.

Some recent work by Kendall and Chinn concerning destruction of vitamin C in the gastrointestinal tract is discussed fully in a recent editorial²³². The general conclusion drawn from their accumulated evidence is that ability to use ascorbic acid occasionally is shown by certain members of known bacterial species but is not a common property of any known species. They found that certain bacteria in the gastrointestinal tract are capable of destroying ascorbic acid and thus preventing normal absorption of this vitamin. They found that the presence of even small amounts of dextrose definitely postponed destruction of ascorbic acid, and since citrus fruits are rich in simple sugars it seems

229 The Nonproprietary Name "Cevitamic Acid" Abandoned for "Ascorbic Acid," Report of the Council on Pharmacy and Chemistry, J A M A **112** 2420 (June 10) 1939

230 Ecker, E E, Pillemer, L, Griffiths, J J, and Schwartz, W P. Complement and Ascorbic Acid in Human Scurvy. An Experimental Study, J A M A **112** 1449-1452 (April 15) 1939

231 Madison, R R, Fish, M, and Frick, O. Vitamin-C Inhibition of Agglutinin Production, Proc Soc Exper Biol & Med **39** 545-547 (Dec) 1938. Cameron, G D W. Antitoxin Response in Guinea Pigs Deficient in Vitamin C, Canad Pub Health J **29** 404-406 (Aug) 1938, abstracted, Nutrition Abstr & Rev **8** 651 (Jan) 1939. Heise, F H, and Steenken, W, Jr. Vitamin C and Immunity in Tuberculosis of Guinea Pigs, Am Rev Tuberc **39** 794-795 (June) 1939.

232 Destruction of Vitamin C in the Gastrointestinal Tract, editorial, J A M A **111** 2395-2396 (Dec 24) 1938

probable that these sugars deflect microbic attacks on ascorbic acid as long as the sugars are present in the digestive tract. Whether or not cane sugar added to fruit further inhibits destruction of the vitamin was not determined.

Sendroy and Miller²³³ made a study of renal function as a factor which may influence the urinary excretion of ascorbic acid. They found that abnormally slow excretion of administered ascorbic acid does not indicate necessarily a low bodily content of vitamin C if renal function is decreased. Renal damage retards excretion even when no deficit of vitamin C exists. They found that the effect of a lowering of renal function on ascorbic acid clearance runs approximately parallel to the effect on urea clearance. Ralli and her associates²³⁴ presented evidence which indicates that vitamin C is excreted by filtration and active tubular reabsorption, and Evans²³⁵ suggested that vitamin C possesses a diuretic property.

Methods of Measuring Ascorbic Acid—Several new procedures for measuring ascorbic acid in the urine and blood have been described recently,²³⁶ and several authors have criticized severely the intradermal injection of 2,6-dichlorophenolindophenol as a reliable guide to the general nutritional status of the body with regard to vitamin C.²³⁷ Chinn and Farmer²³⁸ described a method for estimating ascorbic acid in feces, and by the use of this method the fecal content of the normal person on an adequate but unsupplemented diet is shown to average about 5 mg daily. The ascorbic acid content of plasma, urine and feces of a normal person was studied by these authors after administration of varying amounts of ascorbic acid by mouth. Large variations in the dietary

233 Sendroy, J., Jr., and Miller, B. F. Renal Function as a Factor in the Urinary Excretion of Ascorbic Acid, *J Clin Investigation* **18** 135-140 (Jan) 1939

234 Ralli, E. P., Friedman, G. J., and Rubin, S. H. The Mechanism of the Excretion of Vitamin C by the Human Kidney, *J Clin Investigation* **17** 765-770 (Nov) 1938

235 Evans, W. Vitamin C in Heart Failure, *Lancet* **1** 308-309 (Feb 5) 1938

236 Roe, J. H., and Hall, J. M. The Vitamin C Content of Human Urine and Its Determination Through the 2,4-Dinitrophenylhydrazine Derivative of Dehydroascorbic Acid, *J Biol Chem* **128** 329-337 (April) 1939

237 Goldsmith, G. A., Gowe, D. F., and Ogaard, A. T. Determination of Vitamin C Nutrition by Means of a Skin Test. A Critical Evaluation, *Proc Soc Exper Biol & Med* **41** 370-374 (June) 1939. Wright, I. S., and MacLenathen, E. Excretion of Vitamin C in Sweat, *J Lab & Clin Med* **24** 806-807 (May) 1939

238 Chinn, H., and Farmer, C. J. Determination of Ascorbic Acid in Feces. Its Excretion in Health and Disease, *Proc Soc Exper Biol & Med* **41** 561-566 (June) 1939

intake were shown to affect the fecal excretion of the vitamin only slightly. Patients suffering from certain gastrointestinal disorders were found to excrete larger quantities of ascorbic acid in the feces than normal persons.

Ascorbic Acid Requirements of Man—The question of the exact requirements of man for ascorbic acid is still much debated, and the problem of saturation of the body with vitamin C is still a source of confusion. Kellie and Zilva²³⁹ pointed out that a person may be considered to be "saturated" when the amount of ascorbic acid voided in the urine after continued consumption of a certain dose becomes more or less constant. The first appearance of the acid is not always indicative of saturation. In a case which the authors studied carefully they assumed that the minimal dose necessary to bring about saturation lay between 30 and 50 mg per day. They pointed out, however, that this should not be assumed to be the minimal daily dose necessary to prevent the onset of scurvy or even to maintain good health. They stressed again that no undue clinical significance need be attached to maintaining the condition of saturation. They found that determinations of the level of ascorbic acid in blood made at random did not indicate the degree of saturation of a subject, and further comparison of figures of urinary excretion indicated that there is no constant renal threshold for ascorbic acid. Heinemann²⁴⁰ reported that at least 0.8 mg per kilogram of body weight is the dose of ascorbic acid needed by the healthy adult, although 0.4 mg per kilogram was sufficient to protect against actual scurvy. Belser and her associates²⁴¹ found that the requirement of ascorbic acid to maintain complete saturation for the subjects studied varied from 1 to 1.6 mg per kilogram per day. Rietschel and Mensching²⁴² suggested that the dose of ascorbic acid necessary for the maintenance of good health is much smaller. They pointed out that the human requirement of ascorbic acid is small because of the capacity of this substance to be alternately oxidized and reduced. They stressed the economic inconvenience to Germany of having to supply a requirement of 50 mg per person daily and the desirability of persuading the people that this is not necessary. (Their

239 Kellie, A. E., and Zilva, S. S. The Vitamin C Requirements of Man, *Biochem J* **33** 153-164 (Feb.) 1939.

240 Heinemann, M. Requirements for Vitamin C in Man, *J. Clin. Investigation* **17** 671-676 (Sept.) 1938.

241 Belser, W. B., Hauck, H. M., and Storvick, C. A. A Study of the Ascorbic Acid Intake Required to Maintain Tissue Saturation in Normal Adults, *J. Nutrition* **17** 513-526 (June) 1939.

242 Rietschel, H., and Mensching, J. Experimenteller C-Vitamin-Hunger am Menschen, ein Beitrag zur Frage des C-Vitaminbedarfs, *Klin. Wchnschr* **18** 273-278 (Feb. 25) 1939.

work is based on the fact that one of the authors existed for a period of one hundred days on a diet extremely deficient in vitamin C. The concentration of ascorbic acid in the serum dropped to 0.06 mg per hundred cubic centimeters, but no symptoms of scurvy appeared.) Rall and her associates²⁴³ suggested that 100 mg of ascorbic acid is the optimal daily intake.

It is agreed generally that the requirement of ascorbic acid for pregnant and nursing mothers is considerably greater than that for normal persons. During the past year a tremendous amount of work has been done on this problem. Teel and his associates²⁴⁴ found that the ascorbic acid content of the plasma from the cord blood at birth is from two to four times greater than that of maternal plasma at the time of delivery. These authors made a careful study of the dietary intake of ascorbic acid during pregnancy and of the level of ascorbic acid in maternal plasma and in the cord plasma at the time of birth. They found good correlation between the content of ascorbic acid in the maternal diet and the amount of ascorbic acid in the maternal plasma. Their studies indicated that with a relatively constant intake of ascorbic acid the amount of this vitamin in maternal blood plasma decreases markedly as pregnancy advances. This fact seems to be true whether the dietary intake of ascorbic acid is optimal, suboptimal or deficient. The average amount of ascorbic acid in maternal plasma at the time of delivery was only a little more than half that present during the first twenty-eight weeks of pregnancy.

Further studies by Ingalls and his associates²⁴⁵ showed that saturation of the fetal blood occurs even when the maternal plasma contains less than a third or fourth of the amount of ascorbic acid in the plasma of the infant. Their studies showed further that after birth the breast-fed infant may obtain adequate ascorbic acid at the expense of the mother even though she is on a deficient diet and has a low concentration of ascorbic acid in the plasma. The quantity of ascorbic acid secreted in breast milk was found to vary from 20 to 50 mg per twenty-four hours even when the maternal diet contained no more than 20 mg of ascorbic acid daily. These findings indicate that the increased maternal need

243 Rall, E. P., Friedman, G. J., and Sherry, S. Vitamin C Requirement of Man. Prolonged Study of Daily Excretion and Plasma Concentration of Vitamin C, *Proc Soc Exper Biol & Med* **40** 604-605 (April) 1939.

244 Teel, H. M., Burke, B. S., and Draper, R. Vitamin C in Human Pregnancy and Lactation. I. Studies During Pregnancy, *Am J Dis Child* **56** 1004-1010 (Nov.) 1938.

245 Ingalls, T. H., Draper, R., and Teel, H. M. Vitamin C in Human Pregnancy and Lactation. II. Studies During Lactation, *Am J Dis Child* **56** 1011-1019 (Nov.) 1938.

for ascorbic acid during pregnancy apparently extends into the nursing period as well. Elmby and Becker-Christensen²⁴⁶ suggested that by administering an additional 100 mg of ascorbic acid daily to the mother during the first ten days after delivery the ascorbic acid in her serum and milk can be raised from subnormal to normal levels. Uthelm-Toverud²⁴⁷ gave 75 mg as the daily requirement of pregnant and nursing mothers. Snelling and Jackson²⁴⁸ suggested that artificially fed babies should receive additional ascorbic acid from the time of birth. Chu and his associates²⁴⁹ suggested that a concentration of less than 4 mg per hundred cubic centimeters in the mother's milk indicates that she is deficient in vitamin C. Kenney and Rapoport²⁵⁰ reported that 21 infants with scurvy responded well to doses of crystalline ascorbic acid. Williams and Green,²⁵¹ however, found that children with scurvy responded better to administration of orange juice than to synthetic ascorbic acid. The Council on Foods of the American Medical Association²⁵² reported that fresh orange juice retains 97 per cent of its active ascorbic acid after twenty-four hours in the refrigerator protected from air, but that solutions prepared from crystalline ascorbic acid may lose considerable potency under the same conditions.

Clinical Use of Vitamin C—There have been a number of reports during the past year concerning the use of vitamin C in various ophthalmologic conditions. From study of a rather large group of patients, Bouton²⁵³ reported that ascorbic acid deficiency can be held at least

246 Elmby, A, and Becker-Christensen, P. Ascorbic Acid Metabolism in Pregnancy, Labor and Puerperium and During Infant's First Days of Life. *Ugeskr f læger* **100** 1045-1051 (Sept 15) 1938, abstracted, *J A M A* **111** 2252 (Dec 10) 1938.

247 Uthelm-Toverud, K. The Vitamin C Requirements of Pregnant and Lactating Women, *Ztschr f Vitaminforsch* **8** 237-248, 1939, abstracted, *Nutrition Abstr & Rev* **9** 189-190 (July) 1939.

248 Snelling, C E, and Jackson, S H. Blood Studies of Vitamin C During Pregnancy, Birth and Early Infancy, *J Pediat* **14** 447-451 (April) 1939.

249 Chu, F T, Woo, T, and Sung, C. A Study of Vitamin C Metabolism in Lactating Mothers, *Chinese J Physiol* **13** 383-394 (Dec 30) 1938.

250 Kenney, A S, and Rapoport, M. Studies in the Use of Crystalline Vitamin C (Ascorbic Acid) in the Prophylaxis and Treatment of Infantile Scurvy and Some Other Disorders of Infancy and Childhood, *J Pediat* **14** 161-182 (Feb) 1939.

251 Williams, S, and Green, M. Studies in the Urinary Excretion of Vitamin C in Certain Diseases of Children, *M J Australia* **1** 145-150 (Jan 28) 1939.

252 The Loss of Vitamin C in Orange Juice on Standing, Report of the Council on Foods, *J A M A* **112** 2420-2421 (June 10) 1939.

253 Bouton, S M, Jr. Vitamin C and the Aging Eye. An Experimental Clinical Study, *Arch Int Med* **63** 930-945 (May) 1939.

partly responsible for the impairment of vision associated with senescence of the human eye and that administration of ascorbic acid by mouth in adequate doses can counteract this process if the crystalline lens is not principally involved. Ascorbic acid, he found, had no effect on the lens after senile changes had set in. In view of these findings the report by Corkill²⁵⁴ is interesting. His patient, a young Sudanese, was exposed to the severe environment of the desert on a diet particularly lacking in ascorbic acid. In a period of three months arcus senilis but no scurvy developed. This author suggested that arcus senilis is a sign of chronic deficiency of ascorbic acid.

Several reports²⁵⁵ have appeared which indicate that patients with tuberculosis have a greatly increased requirement for ascorbic acid, their daily consumption is from three to five times as much as that of healthy subjects. There seems to be a certain parallelism between the quantity of ascorbic acid excreted and the activity of the tuberculous process.

In a detailed study by Sebesta and her associates²⁵⁶ data are presented which indicate that the average patient with uncomplicated diabetes mellitus can and does have a normal status in regard to ascorbic acid.

Reports continue to appear concerning the value of ascorbic acid in the treatment of essential hematuria,²⁵⁷ but they are not very convincing. Sabin²⁵⁸ reported that both natural and synthetic ascorbic acid has no effect on the course of experimental poliomyelitis in monkeys.

One of the most interesting new uses of ascorbic acid was reported by Holmes and his associates²⁵⁹. After physical examination of 400 men exposed daily to lead, Holmes and his colleagues made monthly checks on the basophilic degeneration and the degree of stippling as shown by

254 Corkill, N. L. Arcus Senilis as a Sign of Chronic Vitamin C Deficiency, *Ann Trop Med* **32** 333-338 (Dec 21) 1938

255 Weber, H. C-Vitaminstoffwechsel bei Lungentuberkulose, *Wien klin Wchnschr* **51** 1191-1193 (Nov 4) 1938. Warns, E. H. J. Influence of Vitamin C on the Course of Osteo-Arthritic Tuberculosis, *Nederl tijdschr v geneesk* **82** 4426-4434 (Sept 10) 1938, abstracted, *J A M A* **111** 2162 (Dec 3) 1938

256 Sebesta, V., Smith, R. M., Fernald, A. T., and Marble, A. The Vitamin C Status of Diabetic Patients, *New England J Med* **220** 56-60 (Jan 12) 1939

257 Burkland, C. E. Use of Vitamin C in the Treatment of Essential Hematuria. Preliminary Report, *J Urol* **41** 401-405 (March) 1939

258 Sabin, A. B. Vitamin C in Relation to Experimental Poliomyelitis, with Incidental Observations on Certain Manifestations in *Macacus Rhesus* Monkeys on a Scorbutic Diet, *J Exper Med* **69** 507-516 (April) 1939

259 Holmes, H. N., Campbell, K., and Amberg, E. J. The Effect of Vitamin C on Lead Poisoning, *J Lab & Clin Med* **24** 1119-1127 (Aug) 1939. Holmes, H. N., Amberg, E. J., and Campbell, K. Vitamin C Treatment in Lead Poisoning, *Science* **89** 322-323 (April 7) 1939

the blood. Records of these monthly tests were kept throughout the year of observation. During the last three months of this period weekly tests were reported on a group of 34 men, all of whom had symptoms and showed signs of chronic lead poisoning. Half of this group were given 100 mg. of synthetic ascorbic acid daily for several weeks, and the other half continued to take calcium gluconate in addition to 100 mg. of ascorbic acid daily. In general the first group of patients (taking ascorbic acid alone) showed marked improvement. In a week or less after beginning the treatment, most of the men enjoyed normal sleep and lost the irritability and nervousness so common in connection with treatment of lead poisoning with calcium. In the second group (taking ascorbic acid plus calcium) the gain was less marked and rather irregular. The authors postulated that ascorbic acid in some way reacts with toxic lead ions to form a poorly ionized and much less toxic compound. They suggested that men who are exposed to the hazards of lead should include in their diet rich sources of ascorbic acid or else take 50 mg. in supplementary form daily.

VITAMIN D

Chemical and Physiologic Properties—Vitamin D is the one vitamin which is most likely to be deficient in the diet of both the rich and the poor. Apart from egg yolk, herring and canned salmon there is little in the average diet to supply vitamin D, and Lindsay and Mottram,²⁶⁰ taking these facts into consideration have given a number of ingenious recipes in which cod liver oil can be added to the diet in a palatable form.

Vollmer²⁶¹ recently had an opportunity to study the distribution of vitamin D in the body after administration of massive doses. To a 4 year old child, 1,600,000 U. S. P. units of vitamin D was given intramuscularly three and one-half days before death and an additional 1,000,000 units of vitamin D thirty-six hours before death. Most of the vitamin D was found to be stored in the skin, liver and brain, and smaller amounts were found in the lungs, spleen and bones. In experimental animals massive doses of vitamin D have been found to produce certain pathologic changes in the kidneys²⁶² and blood vessels.²⁶³ The role of

260 Lindsay, J., and Mottram, V. H. Vitamin D in Diet. Palatable Methods of Supply, *Brit. M. J.* **1** 14-15 (Jan 7) 1939.

261 Vollmer, H. Distribution of Vitamin D in Body After Administration of Massive Doses, *Am. J. Dis. Child.* **57** 343-348 (Feb.) 1939.

262 Harris, R. S., Ross, B. D., and Bunker, J. W. M. Histological Study of Hypervitaminosis D. The Relative Toxicity of the Vitamin D of Irradiated Ergosterol and Tuna Liver Oil, *Am. J. Digest. Dis.* **6** 81-83 (April) 1939.

263 Goormaghtigh, N., and Handovsky, H. Effect of Vitamin D₂ (Calciferol) on the Dog, *Arch. Path.* **26** 1144-1182 (Dec.) 1938.

vitamin D in the metabolism of calcium and phosphorus still is not established fully. Schneider and Steenbock²⁶⁴ found that in the rat vitamin D induces utilization of phosphorus by bone, which deprives the soft tissues of their supply of phosphorus, which in turn inhibits growth. Connell and Wise²⁶⁵ found that vitamin D decreases high concentrations of serum phosphatase in the growing chick, and Albright and his associates²⁶⁶ made an extensive comparison of the effects of vitamin D, dihydrotachysterol and parathyroid extract on the disordered metabolism of patients with rickets. The data presented by these authors are shown in table 3.

A detailed study of the physiologic and pathologic effects of vitamin D is given in a monograph by Rominger²⁶⁷.

Use of Vitamin D in Rickets—Rickets still presents an enigma. Foldes²⁶⁸ emphasized that the problem of rickets is far from being simply one of vitamin deficiency and suggested that the development

TABLE 3—Summary of Data Presented by Albright and Associates

	Calcium Absorbed	Phosphorus Excreted in Urine
Vitamin D	+++	+
Dihydrotachysterol	+	+++
Parathyroid extract	0	++++

of rickets is due to an interplay of endocrine, general nutritional and vitamin factors. Gridgeman and his associates²⁶⁹ showed that in experimental rickets a low intake of salt mixture will produce healing even

264 Schneider, H., and Steenbock, H. A Low Phosphorus Diet and the Response of Rats to Vitamin D₂, *J Biol Chem* **128** 159-171 (April) 1939.

265 Correll, J. T., and Wise, E. C. Studies on the Relative Efficiency of Vitamin D from Several Sources. Influence of Vitamin D of Different Origins on the Serum Phosphatase of the Chicken, *J Biol Chem* **126** 581-588 (Dec) 1938.

266 Albright, F., Sulkowitch, H. W., and Bloomberg, E. A Comparison of the Effects of Vitamin D, Dihydrotachysterol (A. T. 10), and Parathyroid Extract on the Disordered Metabolism of Rickets, *J Clin Investigation* **18** 165-169 (Jan) 1939.

267 Rominger, E. Physiologie und Pathologie des D-Vitamins, *Ergebn d Vitamin- u Hormonforsch* **2** 104-159, 1939.

268 Foldes, E. Is Rickets Due Simply to a Vitamin Deficiency? *Acta paediat* **23** 178-182 (Dec 31) 1938.

269 Gridgeman, N. T., Lees, H., and Wilkinson, H. The Biological Vitamin D Assay of Low-Potency Materials with Special Reference to the Role of the Mineral Content of the Diet, *Biochem J* **33** 645-654 (May) 1939.

in the absence of vitamin D. It generally is conceded, as pointed out by Lewis,²⁷⁰ that the vitamin D content of irradiated milk, although adequate to protect the average infant against rickets, will not afford protection to premature infants, twins or rapidly growing infants. This author found that a dose of vitamin D₂ administered in milk was several times more effective than the same dose given in an oily vehicle. This work was based on the treatment of 21 rachitic infants.

Reports continue to appear which show that rickets and tetany can be cured by oral administration of one single dose of vitamin D (600,000 U. S. P. units of vitamin D₂).²⁷¹ Harnapp²⁷² found vitamin D₃ effective in a single oral dose of from 5 to 10 mg. Brockmann²⁷³ found 15 mg. of vitamin D₂ or D₃ to be effective in curing rickets when given in a single dose. None of these authors noted any ill effects. Gill²⁷⁴ described 4 cases of rickets in which no form of any therapy given over a period of several weeks produced any evidence of healing.

Use of Vitamin D in Other Conditions—Knapp²⁷⁵ reported that vitamin D is useful in the treatment of keratoconus, and King and Hamilton²⁷⁶ reported on its value in the control of pemphigus. Brandaleone²⁷⁷ stated that the local application of cod liver oil in addition to the usual forms of therapy is of considerable value in the treatment of ulcers occurring in diabetes mellitus.

270 Lewis, J. M. Vitamin D Therapy in Children, *M. Clin. North America* **23** 687-696 (May) 1939, The Influence of the Menstruum on the Effectiveness of Vitamin D Obtained from the Livers of the Percomorphi Order of Fish, *J. Pediat.* **14** 559-569 (May) 1939.

271 Vollmer, H. Treatment of Rickets and Tetany with a Single Massive Dose of Vitamin D. Vitamin D Shock Therapy, *J. Pediat.* **14** 491-501 (April) 1939.

272 Harnapp, G. O. Die Stossprophylaxe der Rachitis, *Deutsche med. Wchnschr.* **64** 1835-1837 (Dec. 16) 1938.

273 Brockmann, H. Zur Therapie und Prophylaxe der Rachitis mit einmaliger Stossdosis von Vitamin D₂ und D₃, *Ztschr. f. Kinderh.* **60** 359-370 (Dec. 19) 1938.

274 Gill, A. M. Vitamin-Resistant Rickets, *Arch. Dis. Childhood* **14** 50-63 (March) 1939.

275 Knapp, A. A. Results of Vitamin-D-Complex Treatment of Keratoconus. Preliminary Study, *Am. J. Ophth.* **22** 289-292 (March) 1939.

276 King, H., and Hamilton, C. M. Pemphigus Controlled by Vitamin D, *Arch. Dermat. & Syph.* **39** 515-517 (March) 1939.

277 Brandaleone, H. The Effect of the Direct Application of Cod Liver Oil upon the Healing of Ulcers of the Feet in Patients with Diabetes Mellitus, *Ann. Surg.* **108** 141-152 (July) 1938.

VITAMIN E

Chemical and Physiologic Properties—Recent advances in the chemical study of vitamin E have been considered in a review by Bacharach²⁷⁸ Emerson and his associates²⁷⁹ reported that gamma tocopherol is approximately equal in vitamin potency to beta tocopherol and is definitely a more powerful antioxidant

In an extensive study Barrie²⁸⁰ showed that in rats on a diet partially deficient in vitamin E the length of gestation bears an inverse relation to the amount of vitamin E in the diet In addition paralysis among young rats owing to vitamin E deficiency of the mother rat is the result of the inability of the mother rat to secrete vitamin E in the milk This paralysis can be cured by administration of vitamin E Muller²⁸¹ reported that vitamin E is also secreted in human milk According to Barrie,²⁸² prolonged vitamin E deficiency caused fibrosis of the uterine muscle in rats, and in a certain number of animals leiomyoma developed

Evans and Emerson²⁸³ and Dingemans and van Eck²⁸⁴ were unable to confirm previous reports that tumors were produced in rats by giving large doses of wheat germ oil for long periods These two groups of workers were unable to produce abdominal neoplasms with such treatment

Several groups of workers²⁸⁵ have been able to produce muscular dystrophy by maintaining animals on diets deficient in vitamin E from birth Recovery was produced by administering vitamin E, but function remained impaired Mackenzie and McCollum^{285c} found that alpha

278 Bacharach, A L Recent Research on Vitamin E, *Nutrition Abstr & Rev* **7** 811-822 (April) 1938

279 Emerson, O H , Emerson, G A , and Evans, H M The Occurrence of Gamma Tocopherol in Corn Embryo Oil, *Science* **89** 183 (Feb 24) 1939

280 Barrie, M M O The Effect of Vitamin E Deficiency on the Rat I Duration of Gestation, *Biochem J* **32** 1467-1473 (Sept) 1938, II Lactation, *ibid* **32** 1474-1478 (Sept) 1938

281 Muller, C Ueber den Antisterilitätsfaktor (Vitamin E) in der Frauenmilch, *Schweiz med Wchnschr* **66** 1164-1165 (Nov 21) 1936

282 Barrie, M M O Vitamin E Deficiency in the Rat, Fertility in the Female, *Biochem J* **32** 2134-2137 (Dec) 1938

283 Evans, H M, and Emerson, G A Failure to Produce Abdominal Neoplasms in Rats Receiving Wheat Germ Oil Extracted in Various Ways, *Proc Soc Exper Biol & Med* **41** 318-320 (June) 1939

284 Dingemans, E, and van Eck, W F Wheat Germ Oil and Tumor Formation, *Proc Soc Exper Biol & Med* **41** 622-624 (June) 1939

285 (a) Knowlton, G C, and Hines, H M Effect of Vitamin E Deficient Diet upon Skeletal Muscle, *Proc Soc Exper Biol & Med* **38** 665-667 (June) 1938 (b) Knowlton, G C , Hines, H M, and Brinkhous, K M Effect of Wheat Germ Oil upon E-Deficient Muscular Dystrophy, *ibid* **41** 453-456 (June) 1939 (c) Mackenzie, C G, and McCollum, E V Vitamin E and Nutritional Muscular Dystrophy, *Science* **89** 370-371 (April 21) 1939

tocopherol was one of the factors deficiency of which is involved in causing experimental muscular dystrophy in rabbits. Verzar²⁸⁶ made similar observations and showed further that it is possible to counteract the creatinuria of animals with muscular dystrophy by means of a synthetic vitamin E.

Clinical Application of Vitamin E—Widenbauer,²⁸⁷ over a period of two years, treated 17 premature infants with wheat germ oil, 2 premature infants serving as controls were given olive oil. Eleven of the 17 premature infants who were given vitamin E gained rapidly after previous arrest of growth. However, this small amount of material does not permit definite conclusions.

In a round table discussion of vitamin E, Browne²⁸⁸ pointed out that if all the reports concerning the use of vitamin E in cases of human abortion are taken together, it is apparent that the use of wheat germ oil in habitual abortion is successful in about 75 to 80 per cent of the cases. This appears convincing, but equally good or better results have been obtained by other methods of treatment. Browne reported the following experience in 18 cases of habitual abortion. Eight of the patients were treated with progesterin and 3 with vitamin E, 7 received no treatment. In no instance was there an abortion in the treated patients, but all 7 of the untreated control patients also obtained living children at term. The statement of Wilbur that at present there is no direct evidence that vitamin E is connected with human metabolism still stands.

VITAMIN K

Chemical and Physiologic Properties—Much has been added to our knowledge of the chemical properties of vitamin K. In May 1939 McKee and his associates²⁸⁹ reported the isolation of vitamin K₁ from alfalfa and vitamin K₂ from putrefied fish meal and presented evidence to indicate a quinonoid structure for these vitamins, further work has

286 Verzar, F. Kreatinurie bei Mangel an Vitamin E und ihre Heilung durch dl- α -Tocopherol, Schweiz med Wchnschr **69** 738-741 (Aug 19) 1939, abstracted, J A M A **113** 1448 (Oct 7) 1939.

287 Widenbauer, F. Versuche mit Weizenkeimol (Vitamin E) bei der Aufzucht von Frühgeburten, Ztschr f Kinderh **60** 216-221 (Oct 15) 1938.

288 Browne, F. J. Discussion on Vitamin E, Proc Roy Soc Med **32** 863-864 (June) 1939.

289 McKee, R. W., Binkley, S. B., MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A. The Isolation of Vitamins K₁ and K₂, J Am Chem Soc **61** 1295 (May) 1939.

substantiated these preliminary statements²⁹⁰ Almquist and Klose²⁹¹ reported recently that phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) possesses physical and chemical properties similar to pure vitamin K₁. It has been shown by Almquist and Klose that phthiocol when given at a level of 20 mg per kilogram of diet is effective in preventing hemorrhagic diathesis in chicks existing on a diet deficient in vitamin K. They as well as Ansbacher and Fernholz²⁹² agreed that the activity of phthiocol is lower than that of the more complex form of vitamin K existing in alfalfa.

Thayer and his associates²⁹³ and MacCorquodale and his co-workers²⁹⁴ reported the structure of the vitamin K₁ molecule to be 2-methyl-3-phytyl-1,4-naphthoquinone, and further work by Binkley and his associates²⁹⁵ confirmed through synthesis this report of the structural form of vitamin K₁. Their experiments demonstrated conclusively that the formula 2-methyl-3-phytyl-1,4-naphthoquinone is correct. This work has been confirmed by Fieser and his associates,²⁹⁶ who also described the synthesis of vitamin K₁. Fieser and his co-workers suggested also that vitamin K₂ is 2,3-difarnesyl-1,4-naphthoquinone. Several groups of workers²⁹⁷ demonstrated that 2-methyl-1,4-naphthoquinone possesses high antihemorrhagic activity, and Thayer suggested that since the activity of 2-methyl-1,4-naphthoquinone is approximately equal to that of pure vitamin K₁, it be adopted as a basic standard for assay of vitamin K. The compound does have desirable qualities for standardization in that it is readily obtainable in a satisfactory state of purity, possesses a definite melting point for characterization and is relatively stable when protected from excessive exposure to light. The

290 Binkley, S. B., MacCorquodale, D. W., Cheney, L. C., Thayer, S. A., McKee, R. W., and Doisy, E. A. Derivatives of Vitamins K₁ and K₂, *J. Am. Chem. Soc.* **61** 1612-1613 (June) 1939.

291 Almquist, H. J., and Klose, A. A. The Anti-Hemorrhagic Activity of Pure Synthetic Phthiocol, *J. Am. Chem. Soc.* **61** 1611 (June) 1939.

292 Ansbacher, S., and Fernholz, E. Simple Compounds with Vitamin K Activity, *J. Am. Chem. Soc.* **61** 1924-1925 (July) 1939.

293 Thayer, S. A., Cheney, L. C., Binkley, S. B., MacCorquodale, D. W., and Doisy, E. A. Vitamin K Activity of Some Quinones, *J. Am. Chem. Soc.* **61** 1932 (July) 1939.

294 MacCorquodale, D. W., Binkley, S. B., Thayer, S. A., and Doisy, E. A. On the Constitution of Vitamin K₁, *J. Am. Chem. Soc.* **61** 1928-1929 (July) 1939.

295 Binkley, S. B., MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A. The Isolation of Vitamin K₁, *J. Biol. Chem.* **130** 219-234 (Sept.) 1939.

296 Fieser, L. F., Bowen, D. M., Campbell, W. P., Fieser, M., Fry, E. M., Jones, R. N., Riegel, B., Schweitzer, C. E., and Smith, P. G. Quinones Having Vitamin K Activity, *J. Am. Chem. Soc.* **61** 1925-1926 (July) 1939.

297 Thayer and others²⁹³ MacCorquodale and others²⁹⁴

same workers suggested that by adopting this substance as the standard for assay the unit could be defined in terms used by the League of Nations' Committee as the specific vitamin K activity of 1 microgram of pure 2-methyl-1,4-naphthoquinone

Little is known about the physiologic effect of vitamin K. Greaves²⁹⁸ demonstrated that bile is essential for its absorption and that in animals subsisting on a diet deficient in vitamin K bile alone has no effect on the hemorrhagic tendency, whereas vitamin K plus bile salts has immediate effect. This author has found that concentrates of vitamin K are effective in the rat when administered either subcutaneously or intraperitoneally. Greaves²⁹⁹ also pointed out that although many fat-soluble vitamins are stored in large amounts in the body and held in reserve for times of need, this is not true of vitamin K.

The exact mode of action of vitamin K is not known. It has been suggested that vitamin K acts as a necessary building stone for the formation of prothrombin, and others have suggested that it is carried as a prosthetic group on the prothrombin molecule. Dam and his associates³⁰⁰ showed that vitamin K in concentrated form does not contribute in vitro to the coagulability of blood or plasma from K-avitaminotic chicks. They further demonstrated that removal of the spleen does not alter the response of K-avitaminotic birds to the vitamin. Warner³⁰¹ reported that partial hepatectomy in animals results in a decrease in the concentration of prothrombin in the circulating blood and that the decrease in prothrombin is, to some extent, correlated with the amount of liver removed. Rhoads and his associates³⁰² demonstrated that hepatectomy in dogs results in a rapid fall of the level of prothrombin in the circulating blood.

Methods of Measuring Prothrombin—To use vitamin K intelligently, the physician must have a satisfactory method of measuring the concentration of prothrombin in the circulating blood. Four methods, all of them indirect and not entirely satisfactory on physiologic grounds,

298 Greaves, J. D. The Nature of the Factor Which Is Concerned in Loss of Blood Coagulability of Bile Fistula in Jaundiced Rats, *Am J Physiol* **125** 423-438 (March) 1939

299 Greaves, J. D., in discussion on Butt, H. R., Snell, A. M., and Osterberg, H. E. The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, *J A M A* **113** 383-390 (July 29) 1939

300 Dam, H., Glavin, J., Lewis, L., and Tage-Hansen, E. Studies on the Mode of Action of Vitamin K, *Scandinav Arch f Physiol* **79** 121-133 (Aug) 1938

301 Warner, E. D. Plasma Prothrombin. Effect of Partial Hepatectomy, *J Exper Med* **68** 831-835 (Dec) 1938

302 Warren, R., and Rhoads, J. E. The Hepatic Origin of the Plasma-Prothrombin Observations After Total Hepatectomy in the Dog, *Am J M Sc* **198** 193-197 (Aug) 1939

are now available. The first is the method of Quick and his associates,³⁰³ which is well adapted for the clinical laboratory and is at present used widely. The second method, that of Warner and his associates,³⁰⁴ measures the concentration of prothrombin quantitatively and is adapted generally only to the resources of a large laboratory with a staff of expertly trained technicians. A third method, developed by Dam and others,³⁰⁵ is a modification of that of Fisher and depends somewhat on the same principle as that of Quick and his associates. This method has not been used generally in this country. The fourth method, developed by Ziffren and his co-workers,³⁰⁶ is a simple bedside method of comparing the clotting time of normal blood with that of the specimen in question after thromboplastin has been added to each. The unknown is expressed in percentage of the normal. It should be emphasized that the choice of the most effective method depends somewhat on the experience and facilities of the physician concerned.

Clinical Applications—It has now been well established in this country and abroad that concentrates containing vitamin K or pure synthetic products exhibiting a high antihemorrhagic activity are useful in elevating the level of prothrombin in the circulating blood of patients who exhibit hypoprothrombinemia.³⁰⁷ These several articles indicate

303 Quick, A. J., Stanley-Brown, M., and Bancroft, F. W. A Study of the Coagulation Defect in Hemophilia and in Jaundice, *Am J M Sc* **190** 501-511 (Oct.) 1935

304 Warner, E. D., Brinkhous, K. M., and Smith, H. P. A Quantitative Study on Blood Clotting. Prothrombin Fluctuations Under Experimental Conditions, *Am J Physiol* **114** 667-675 (Feb.) 1936

305 Dam, H., Glavind, J., Lewis, L., and Tage-Hansen, E. Studies on the Mode of Action of Vitamin K, *Scandinav Arch f Physiol* **79** 121-133, 1938

306 Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P. Control of Vitamin K Therapy. Compensatory Mechanisms at Low Prothrombin Levels, *Proc Soc Exper Biol & Med* **40** 595-597 (April) 1939

307 (a) Butt, H. R., Snell, A. M., and Osterberg, A. E. The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, *J A M A* **113** 383-390 (July 29) 1939. (b) Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R. Clinical and Experimental Studies on Vitamin K, *ibid* **113** 380-383 (July 29) 1939. (c) Dam, H., and Glavind, J. The Clotting Power of Human and Mammalian Blood in Relation to Vitamin K, *Acta med Scandinav* **96** 108-128, 1938. (d) Stewart, J. D. Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, *Ann Surg* **109** 588-595 (April) 1939. (e) Rhoads, E. J. The Relation of Vitamin K to the Hemorrhagic Tendency in Obstructive Jaundice, with a Report of Cerophyl as a Source of Vitamin K, *Surgery* **5** 794-808 (May) 1939. (f) Clark, R. L., Jr., Dixon, C. F., Butt, H. R., and Snell, A. M. Deficiency of Prothrombin Associated with Various Intestinal Disorders. Its Treatment with the Antihemorrhagic Vitamin (Vitamin K), *Proc Staff Meet, Mayo Clin* **14** 407-416 (June 28) 1939

that a deficiency of prothrombin exists in a number of conditions which can be corrected by the administration of vitamin K. A deficiency of prothrombin apparently may occur in the following groups

1 Human beings who are on a diet inadequate in vitamin K

2 Newborn infants Waddell and his associates³⁰⁸ reported a fairly common deficiency of prothrombin which responds to the administration of vitamin K by mouth, the mechanism of which is not entirely clear

3 Persons in whom intestinal absorption is inadequate owing to (a) lack of bile in the intestine in consequence of poor secretion of bile salts, (b) various intestinal lesions and (c) obstruction of the bile ducts from any cause

4 Persons with primary hepatic injury There is considerable evidence to indicate that the liver plays an active part in the formation of prothrombin, and injury of that organ can be the cause of a deficiency of prothrombin. In patients with primary hepatic disease several authors have noted poor response to even large doses of vitamin K administered orally, intramuscularly or intravenously

In the early work on vitamin K, concentrates of alfalfa were administered together with bile salts by mouth, and in a few instances these oily concentrates were administered intramuscularly. Using these methods of administration, Butt and his associates^{307a} reported that none of the 127 patients with jaundice who received this medication had any untoward reactions, although doses as large as 20 Gm. were administered at one time. In most of these cases in which hypoprothrombinemia was exhibited a decrease in the prolonged prothrombin clotting time occurred after the administration of concentrates of alfalfa and bile salts. Smith and his associates^{307b} and Stewart^{307d} reported similar observations.

The recent development of synthetic compounds possessing anti-hemorrhagic activity has led to the general use of these materials as a substitute for the concentrates of alfalfa. Smith and his associates³⁰⁹ and Butt and his associates³¹⁰ demonstrated that phthiocol administered

308 Waddell, W. W., Jr., and Guerry, Du P. III. Effect of Vitamin K on the Clotting Time of the Prothrombin and the Blood, with Special Reference to Unnatural Bleeding of the Newly Born, *J. A. M. A.* **112** 2259-2263 (June 3) 1939

309 Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R. Clinical and Experimental Studies on Vitamin K [note at end of paper], *J. A. M. A.* **113** 383 (July 29) 1939

310 Butt, H. R., Snell, A. M., and Osterberg, A. E. Phthiocol. Its Therapeutic Effect in the Treatment of Hypoprothrombinemia Associated with Jaundice, a Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **14** 497-502 (Aug. 9) 1939

by the intravenous route is effective in increasing the level of prothrombin in the circulating blood of patients having hypoprothrombinemia. The 10 patients treated by Butt had no untoward reactions, and the prolonged prothrombin clotting time of all decreased to nearly normal within twelve to twenty-four hours after the administration of phthiocol. Since that report several cases of cirrhosis of the liver have been encountered in which the administration of phthiocol did not result in decreasing the prolonged prothrombin clotting time.

The compound 2-methyl-1,4-naphthoquinone has been found effective in elevating the level of prothrombin in the blood when administered in doses of 1 mg.³¹¹ Other workers³¹² have found this material effective when it is given in doses of 1 to 2 mg. together with 5 to 10 grams (0.3 to 0.65 Gm.) of animal bile salts by mouth to patients with hypoprothrombinemia. In several cases it has been given in doses of 1 mg. with effective response. No untoward reactions were noted when the material was administered by mouth or intravenously.

The synthetic naphthoquinones which have a marked antihemorrhagic activity are definitely easier to handle, and undoubtedly they will eventually replace the older concentrates now employed, however, until these synthetic compounds have had wider clinical usage, it will be best to proceed cautiously.

• GENERAL FEATURES IN NUTRITION

The reports on vitamins during the past year have indicated clearly that many act in fundamental biologic processes as factors in oxidation and reduction and that some of these necessary substances as they occur in food are not vitamins in their final forms but are precursors of the true vitamins. There has been much experimental evidence from nutritional laboratories. Although this work has pointed the way, the reports must be scrutinized carefully. It has been well established that such results may not in every case unequivocally link the substance with deficiency in man. Russell³¹³ pointed out that the simplest and most fundamental fact that can be stated with regard to the relation of vitamins to disease is that a given vitamin will not cure a deficiency caused by the lack of another vitamin. There is little doubt that clinical

311 Fernholz, E., and Ansbacher, S. Vitamin K Activity of Synthetic Phthiocol, *Science* **90** 215 (Sept. 1) 1939.

312 Butt, H. R., Snell, A. M., Osterberg, A. E., and Bollman, J. L. Unpublished data.

313 Russell, W. C. Vitamins in the Nutrition of Animals, *J. Am. Vet. M. A.* **94** 81-89 (Feb.) 1939.

observation is one of the most important factors in recognizing deficiency diseases. However, the rapid progress in the chemical and biologic assays of various vitamins gives hope that such methods will provide valuable aids for diagnosis in vitamin deficiencies.

Little is known of dietary requirements in disease with reference to the vitamins. It appears that the normal resistance of the human organism to some vitamin deficiencies is remarkable. In fact, it appears almost that some independent disease must be acquired before avitaminosis becomes manifest. Obviously the vitamin needs of the body in disease are very different from those in health, and it is well recognized that the absorption of vitamins may be altered in pathologic conditions of the gastrointestinal tract, by pronounced diuresis or diarrhea, by increased metabolism, by hepatic injury or by obstruction to the flow of bile into the intestinal tract. This interrelation of the vitamins is an interesting and important problem. Collett and Eriksen³¹⁴ found that vitamins A and D have no antagonistic action on vitamin C in the guinea pig and that in vitro vitamins A and D have no destructive chemical action on vitamin C. However, large doses of cod liver oil were found to inhibit the antiscorbutic action of vitamin C.

Fortification of Foods—The second portion of the recent report by the Council of Pharmacy and Chemistry and the Council on Foods of the American Medical Association³¹⁵ dealt with the fortification of foods with vitamins. Three years ago these councils decided that the general and indiscriminate fortification of foods with vitamins as well as with minerals should be discouraged. At that time numerous products were advertised, with much stress being placed on their fortification with various health-giving, "pep"-giving vitamins. The councils had to frown on such indiscriminate fortifications, mainly because the items selected for fortification, such as candy, whisky and pop, are not recognized as normal carriers of vitamins.

It is obvious that improvement of foods should not be prohibited, but the Council on Foods remains of the opinion that fortification with vitamins and minerals should be controlled. There are several reasons for this stand. 1. Even the requirements of the vitamins of known significance in human nutrition are still under investigation, and the optimal quantities of any of them are far from being established. 2.

314 Collett, E, and Eriksen, B. Interrelations of the Vitamins, *Biochem J* **32** 2299-2303 (Dec.) 1938.

315 The Status of Certain Questions Concerning Vitamins Based on Recommendations of the Cooperative Committee on Vitamins, Report of Council of Pharmacy and Chemistry and Council on Foods, *J A M A* **113** 589-595 (Aug 12) 1939.

Although dietary deficiencies are not limited to any one group, they are certainly most likely to appear among persons with low incomes, and in fortifying any food consideration of the cost should be given careful thought, since a higher cost of the product may defeat the purpose of fortification.

Several recent reports indicate that if the average diet is carefully selected adequate amounts of minerals and vitamins are likely to be present. Prouty and Cathcart³¹⁶ in an extensive study of the 39 most popular commercial loaves of white bread from 33 bakeries in 27 states reported that the average percentage of calcium found was nearly three times that reported by previous investigators. They pointed out that the increased use of milk solids and yeast foods has increased considerably the calcium content of commercial white bread. On the basis of their results, six slices of average commercial white bread will supply approximately 30 per cent of the daily requirement of calcium of the average adult, provided the total amount of calcium is assimilated. In England, Copping³¹⁷ is of a different opinion. He concluded that in order to regain all that has been lost by the ultramilling of flour the population must change back to whole meal. This, of course, necessitates altering the tastes of the people and overcoming the vested interest in the existing milling industry. The advantage to be gained in national health would probably make such a tremendous undertaking well worth while, but it seems now that discriminate fortification with vitamins and minerals may offer a solution more readily obtainable. Many feel with Elvehjem³¹⁸ that "this country is still sufficiently agricultural to produce the foods adequate for a normal diet, so that we may consume pleasing foods rather than obtaining our vitamins from the drug store except in emergencies."

The present attitude of the Council on Foods³¹⁹ is given in the following statement taken from the minutes of its annual meeting:

The Council on Foods desires to encourage the restorative addition of vitamins or minerals or other dietary essentials, in such amounts as will raise the content of vitamin or mineral or other dietary essential of general purpose foods to recognized high natural levels, with the provision that such additions are to be limited to vitamins or minerals or other dietary essentials, for which a wider distribution is considered by the Council to be in the interest of the public health.

316 Prouty, W. W., and Cathcart, W. H. The Calcium Content of White Bread, *J. Nutrition* **18** 217-226 (Sept. 10) 1939.

317 Copping, A. M. The Nutritive Value of Wheaten Flour and Bread, *Nutrition Abstr. & Rev.* **8** 555-566 (Jan.) 1939.

318 Elvehjem, C. A. Nicotinic Acid in Nutrition, *Ann. Int. Med.* **13** 225-231 (Aug.) 1939.

319 Report of the Annual Meeting of the Council on Foods, *J. A. M. A.* **113** 680-681 (Aug. 19) 1939.

The Council is opposed to the indiscriminate fortification of general purpose foods with vitamins or minerals or other dietary essentials. By fortification is meant the addition to a food of such an amount of a vitamin or other dietary essential as to make the total content larger than that contained in any natural (unprocessed) food of its class.

The following fortifications are recognized by the Council as being in the interest of the public health: (1) the addition of vitamin D to milk to an extent not to exceed 400 units per quart, no objection being made when the added vitamin is obtained from a natural source, if it carries with it one or more other vitamins, (2) the addition of vitamin A to substitutes for butter to an extent not to exceed the amount of vitamin A in butter of high natural content of vitamin A, no objection being made when the added vitamin is obtained from a natural source, if it carries with it one or more other vitamins, (3) the addition of iodine to table salt in an amount not to exceed one part of sodium or potassium iodide for each 5,000 parts of salt, (4) the addition of calcium salts to wheat flour or other cereal product in an amount such that the calcium content of the finished product does not exceed 0.075 Gm. for each 100 calories, and (5) the addition of iron to wheat flour or other cereal product in an amount such that the iron content of the finished product does not exceed 0.0015 Gm. (15 mg.) for each 100 calories.

News and Comment

Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation—Sixty-two applications for grants were received by the trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation during 1939. Thirty of these came from the United States and the other thirty-two from fourteen different countries in Europe, Asia, Africa, South America and North America. Thirty-two grants were made during the year, one being a continued annual grant.

In the sixteen years of its existence the foundation has made three hundred and seventy-two grants, which have been distributed to investigators in Argentina, Austria, Belgium, Brazil, Canada, Chile, China, Czechoslovakia, Denmark, Egypt, Estonia, Finland, France, Germany, Great Britain, Greece, Hungary, Iraq, Italy, Latvia, Lebanon, Netherlands, North Africa, Norway, Palestine, Poland, Portugal, Rumania, South Africa, Sweden, Switzerland, Syria, Venezuela, Yugoslavia and the United States.

During the present great need for funds, grants will be given in the sciences closely related to medicine without reference to special fields. The maximum grants will usually be less than \$500.

Applications for grants to be held during the year 1940-1941 must be in the hands of the executive committee before April 1940. Letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid, applicants should state whether they have approached other foundations for financial assistance. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only applications complying with the foregoing conditions will be considered.

Applications should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, Mass., U. S. A.

Studies on Pellagra—Dr. V. P. Sydenstricker, professor of medicine at the University of Georgia School of Medicine, was recently awarded a grant of \$6,000 by The John and Mary R. Markle Foundation for the continuation of his studies on pellagra. During the spring Dr. Sydenstricker will present the following papers: "Acute Deficiency Syndromes," at the Johns Hopkins Medical and Surgical Association, Baltimore, February 23, "The Present Status of Nicotinic Acid," at the Federation of American Societies for Experimental Biology, New Orleans, March 15, "The Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency" (clinical lecture), at the American College of Physicians, Cleveland, April 1, "The Relation of Gastrointestinal Disease to Avitaminosis," at the New York Chapter of the American Gastroenterological Association, New York, April 15, and "Multiple Deficiency Features of Pellagra," at the Eighth Pan-American Scientific Congress, Washington, D. C., May 10.

Book Reviews

Immunity Principles and Application in Medicine and Public Health
An Exposition of the Biological Phenomena of Infection and Recovery of the Animal Body from Infectious Disease, with Consideration of the Application of the Principles of Immunity to Diagnosis, Treatment and Prophylaxis and Their Usefulness in the Control of Epidemics By Hans Zinsser, M D, Professor of Bacteriology and Immunology, Harvard Medical School, John F Enders, Ph D, Assistant Professor of Bacteriology and Immunology, Harvard Medical School, and LeRoy D Fothergill, M D, Assistant Professor of Bacteriology and Immunology and Associate in Pediatrics, Harvard Medical School New York The Macmillan Company, 1939

This, the fifth edition of the excellent book originally called "Resistance to Infectious Diseases," constitutes not only a revision but an expansion. In practical development and increasing application in clinical and preventive medicine, immunology has extended beyond the confines of the laboratory and the concern of the pure scientist. Today a knowledge of immunology is essential in the practice of medicine and of public health. Consistent with the rapid growth of the subject, section I, "Principles and Theories," has been revised by the elimination of much outdated material, the modernization of that retained and the addition of the large accumulation of recent years. The expanded section II, "Special Immunological Problems in Individual Infections," is especially worthy of note. This section treats at length the different phases of immunology as they pertain to preventive and curative medicine and diagnosis, comprehending the viruses, rickettsiae, the organisms of syphilis, tuberculosis, diphtheria and anaerobic infections, hemolytic streptococci and staphylococci and the organisms of meningitis, pneumonia and acute intestinal infections. Its utilitarian aspects will prove particularly interesting and valuable to the clinician and none the less important to the specialist. The book may be recommended to the student, laboratory worker and practitioner as an able exposition of immunology.

Necrosis aguda del pancreas (pancreatitis edematosa y hemorrágica)
By Dr Jose M A Delrio Pp 242 Buenos Aires Aniceto Lopez, 1937

The author has written an excellent monograph. The volume is 242 pages in length and has a fine bibliography.

The following conclusions are drawn:

1 Sixty per cent of human beings have a common duct of Wirsung, and the control of the sphincter of Oddi depends on the biliary duodenal reflux.

2 The physiopathologic transformation produced by diseases of the biliary system and duodenum is caused by the failure of the normal defense mechanisms. In 60 per cent of the cases of acute pancreatitis abnormality exists in the biliary tract and duodenum.

3 One is forced to admit the multiplicity of pathogenesis, since in many cases the disease takes a lymphovascular route, while in many cases there exists a concomitant hepatobiliary disease.

4 One admits the existence of edematous pancreatitis of the following origins: idiopathic, lymphovascular, anaphylactic and inflammatory. The so-called edematous and hemorrhagic pancreatitis must be considered as part of the process of necrotic pancreatitis. The first phase is edema and the second more or less extensive necrosis. As a consequence this condition should be called pancreatic necrosis in either an edematous or a hemorrhagic state and for clinical simplicity should be called acute, subacute or chronic pancreatic necrosis.

5 Pancreatic necrosis is a relatively frequent disease

6 It has a characteristic clinical picture, which, however, does not necessarily follow the anatomic-pathologic process present

7 The diagnosis is possible in most cases with the clinical facilities at hand, and only rarely is the picture such as to render the diagnosis impossible

8 The prognosis is usually hopeless when considerable involvement has taken place. It is only relatively favorable for subacute and chronic disease. It depends primarily on the amount of involvement and secondarily on the stage of the disease.

9 Surgical intervention is useless in the acute stages and is considered harmful in the subacute and the chronic stage. Its only indications are the presence of a calculus in the ampulla or evidence of abscess formation. The ideal treatment consists in the treatment of the causes. One should not consider these indications if either a phlegmon or a true gangrene exists when operation is indicated. This also holds true if the process of autodigestion is taking place.

Most of the apparent clinical cures of severe disease are due to an error in diagnosis.

Notices

CUMULATED INDEX OF THE ARCHIVES OF INTERNAL MEDICINE

Requests have been received for a twenty year index of the ARCHIVES OF INTERNAL MEDICINE. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed \$5 a copy. It will be appreciated if those who are interested in such an index will fill out the form which appears below and send it to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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TOXIC HEPATITIS

INTERMEDIARY FATAL FORM WITH ENLARGEMENT OF THE
LIVER, A CLINICAL AND PATHOLOGIC STUDY

J D KIRSHBAUM, M D

AND

H POPPER, M D *

CHICAGO

Toxic hepatitis is known to both clinician and pathologist. Pathologists know the fatal form, acute yellow or red atrophy, characterized grossly by the small atrophic liver and microscopically by necrosis of the liver cells. Clinicians are more familiar with a nonfatal form of hepatitis, of which so-called catarrhal jaundice is typical. In cases of the latter condition the liver is usually enlarged, and since recovery is the usual outcome, knowledge of the pathologic changes is meager, except for a few histologic descriptions which are available from biopsies of the liver or from autopsy in cases of accidental death (Klemperer¹, Schrumph,² Popper,³ Eppinger and his associates⁴ and Aschoff⁵).

Eppinger⁶ was the first to state that catarrhal jaundice is the miniature form of acute yellow atrophy. The few histologic observations available confirm the statement, later supported by Gaskell,⁷ Boyd⁸ and others. Animal experiments with allylformate intoxication by Popper⁹ have revealed the transition from catarrhal jaundice to acute atrophy of the liver.

* Research Fellow in the Cook County Graduate School of Medicine

From the Department of Pathology of the Cook County Hospital and the Cook County Graduate School of Medicine

1 Klemperer, P., Killian, J. A., and Heyd, C. G. Pathology of "Icterus Catarrhalis," Arch Path **2** 631 (Nov.) 1926

2 Schrumph, A. Ann d'anat path **9** 17, 1932

3 Popper, H. Ztschr f klin Med **131** 161, 1937

4 Eppinger, H., Kaunitz, H., and Popper, H. Die seröse Entzündung, Berlin, Julius Springer, 1935

5 Aschoff, L. Verhandl d deutsch Gesellsch f inn Med **44** 261, 1932

6 Eppinger, H. Die Leberkrankheiten, Berlin, Julius Springer 1937

7 Gaskell, J. F. J Path & Bact **36** 257, 1933

8 Boyd, W. The Pathology of Internal Diseases, ed 2, Philadelphia, Lea & Febiger, 1936

9 Popper, H. Wien klin Wchnsch **49** 207, 1936

It is natural, then, to ask what causes the enlargement of the liver in catarrhal jaundice and how the contrast to the smallness of the liver in acute yellow atrophy may be explained

This question prompted our study of a group of 15 cases in which jaundice was fatal. The liver was observed to be enlarged at autopsy, as in catarrhal jaundice, whereas the clinical picture was that of an acute fulminating hepatic disease, with death occurring within a short time, as in cases of acute yellow atrophy of the liver. In a review of the literature and modern textbooks of medicine, one fails to find a thorough description of cases such as ours.

In addition to the reported cases of typical catarrhal jaundice mentioned previously, we have found reference to cases similar to ours in the textbook of Eppinger,⁸ who reviewed 63 cases of clinical acute yellow atrophy. Of this group, he classified 17 as instances of catarrhal jaundice. Histologically, there were 1 case of diffuse serous hepatitis with dissociation, 12 cases of central necrosis, 1 case of peripheral necrosis and 3 cases of fatty degeneration similar to that in phosphorus poisoning. In this series of cases no mention is made of the size of the liver, whether it was enlarged or shrunken.

In 1932 the late Dr Jaffé¹⁰ called attention to a case of acute toxic hepatitis characterized by jaundice of two weeks' duration. At autopsy enlargement of the liver was noted, and microscopic examination showed marked separation of the liver cells and cloudy swelling. From 1929 to 1939, in a series of 12,000 consecutive autopsies at the Cook County Hospital, 15 cases of acute toxic hepatitis with enlargement of the liver were encountered. Excluded from this group were cases of poisoning from drugs, such as arsphenamine and mercury, and cases in which toxic hepatitis was secondary to other conditions, e. g., pneumonia and suppurative processes.

CLINICAL OBSERVATIONS

In our group there were 10 males and 5 females, 6 of the males and 1 of the females were Negroes, the youngest was 10 years of age, the oldest 58. The average duration of illness was nine and a half days, the shortest one day and the longest twenty-one days, in addition, 2 patients had been ill two months and three months, respectively.

Ten patients had symptoms of sudden onset, with chills, fever, vomiting, abdominal pains and jaundice. This was followed by stupor and unconsciousness. Headaches were a frequent complaint. Anuria, which usually occurs with acute yellow atrophy, was observed in 2 patients. Six patients complained of pains in the joints and muscles.

Two of the patients had active gonorrhea and 1 latent syphilis. In 2 there was evidence of disease of the gallbladder two years prior to admission. In 2 patients meningeal symptoms predominated, in 1 of

¹⁰ Jaffé, R. H. Bull. Chicago M. Soc. **35** 312 1932

them meningitis was suspected because of the pains in the neck and slight rigidity, but the result of a spinal puncture proved negative

The diagnosis of acute primary hepatitis was made in 8 cases, while in 1 infectious hepatitis was considered. In 4 cases a mechanical type of jaundice was suggested, in 2, gallstones, and in the other 2, cholecystitis and carcinoma of the liver. In 2 cases uremia was suggested, however, in 1 instance the diagnosis of hepatitis was made prior to death. In 1 the condition was considered to be biliary cirrhosis.

Alcoholism was observed in 2 cases, and paratyphoid B bacilli were isolated from the blood and feces of the child.

The laboratory examination was not always complete, because many of the patients died shortly after admission. The blood showed moderate anemia, the average red cell count was 3,710,000 per cubic millimeter, but it was not characteristic. The white cell count was always high, varying from 11,000 to 38,200 per cubic millimeter. The icteric index varied from 90 to 250, the rise being usually rapid, within a few days. The urea nitrogen varied from 40 to 205 mg per hundred cubic centimeters of blood. In 3 patients the creatinine of the blood fluctuated from 6.66 to 16 mg per hundred cubic centimeters. The Wassermann reaction of the blood was negative in 5 cases, while in 1 there was anatomic evidence of syphilis and in another the Wassermann reaction of the spinal fluid was positive, in 8 cases the blood was not examined. Examination of the urine showed albuminuria, bilirubinuria and casts in the sediment. The stools were examined in 11 cases, in 6 they were clay colored, in 3 green to brown and in 2 tarry.

The temperature varied from 99.6 to 105 F. In 12 cases there was tachycardia (with a rate of from 96 to 135), while in 1 bradycardia (with a rate of 68) was present. The blood pressure was usually low, the systolic varying from 85 to 134 and the diastolic from 52 to 80. Enlargement of the liver was noted in 10 cases, and the spleen was palpated in 5.

ANATOMIC OBSERVATIONS

The liver was enlarged. In the 14 adults the weight varied from 1,480 to 3,640 Gm, the average being 2,150 Gm. The weight of the child's liver was 950 Gm. There was no correlation between the acuteness of the illness and the degree of enlargement of the liver. The capsule was tense, the edges were round, the consistency was firm, and the cut surface was usually grayish brown. The gallbladder in 4 cases showed fibrosis, while in 1 there were stones in the lumen, and in 1 a cholecystectomy had been done. In all cases the extrahepatic bile ducts were free and showed no changes.

The spleens varied in weight from 90 to 690 Gm, with an average of 253 Gm. The weight of the spleen of the child was 200 Gm. The spleen was soft in 11 cases.

The heart was hypertrophic in 4 cases and dilated in 3

The kidneys were usually markedly swollen, the weight varying from 360 to 660 Gm, with an average of 490 Gm. The lungs showed edema in 8 cases, there was catarrh of the gastric mucosa in 2 cases and of the intestine in 5. In only 3 of them was there slight ascites, the fluid

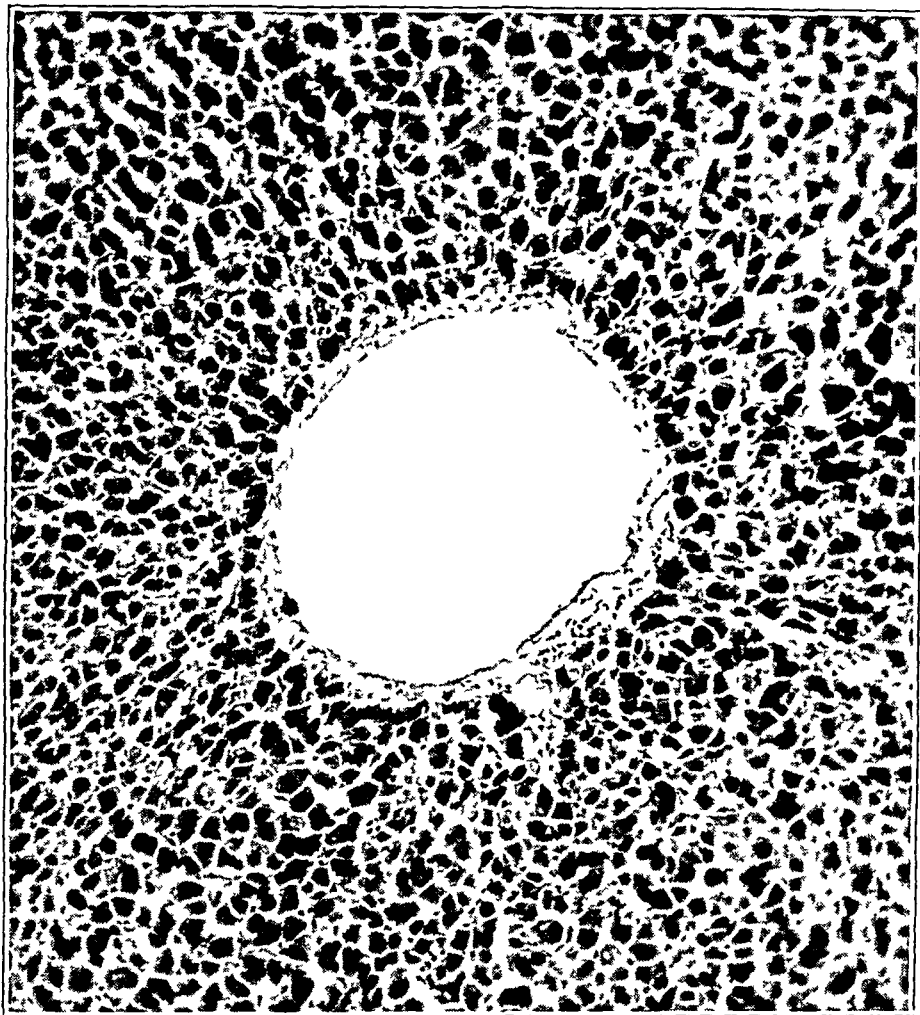


Fig 1—Note the dissociation of the cords of liver cells about a central vein and the normal-staining nuclei (low magnification)

measuring up to 150 cc. In 11 instances there were signs of hemorrhagic diathesis, especially in the skeletal muscles in 2.

In all 15 cases jaundice was marked.

HISTOLOGIC OBSERVATIONS

Thorough histologic studies were made in 13 of the cases. The outstanding observation was moderate to marked interruption of the cords of liver cells, separating single cells or groups of cells (fig 1). The free edges of the cells in the groups showed rounding and as the

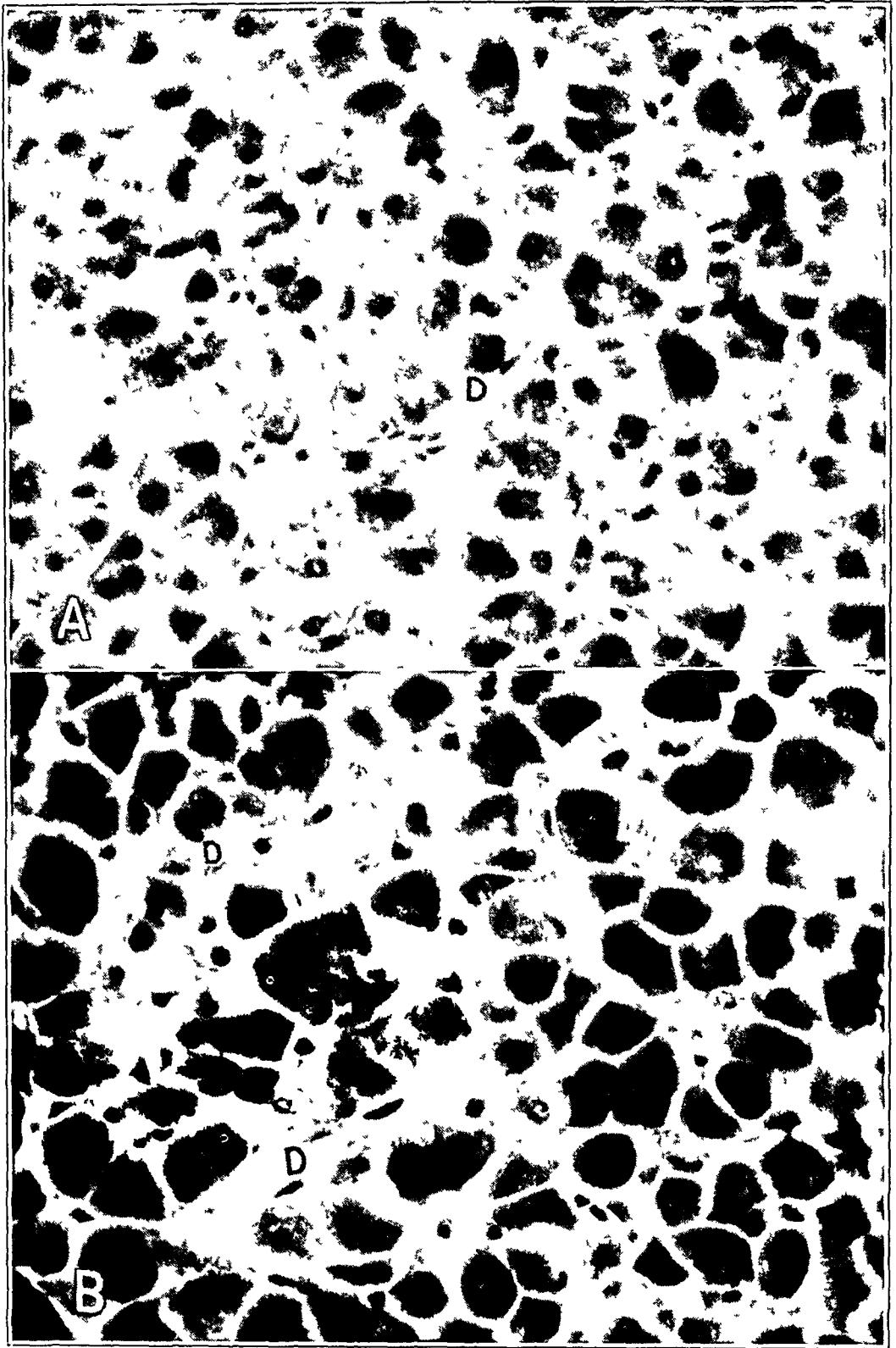


Fig 2—Marked dissociation of liver cells. Note the rounding of the borders of the cells and the widening of the Disse spaces (*D*). The nuclei for the most part are intact. In *A* the process is more severe than in *B*.

cells became entirely separated from one another, they became completely round. However, the nuclei were preserved and took the normal stain. The cytoplasm also appeared to be unchanged, as far as the morphologic picture was concerned (fig 2). The whole phenomenon, which may be described as dissociation, was present in 13 cases and was marked in 7. The changes were not localized and appeared uniformly diffuse.

Furthermore, there was separation of the cords of liver cells as a unit and the walls of the blood capillaries. This space, described by Disse, was thus widened and contained granular masses which stained with eosin. By use of the fluorescence microscope, one of us (H. P.) has shown that the granular masses were plasma proteins and were also found between isolated groups of liver cells. The picture corresponded with that of toxic edema of the liver, or so-called serous hepatitis. It was present in 11 cases and was marked in 7.

Another significant observation was the changes in the liver cells about the central veins, such as shrinking of the cell with pyknosis and granular alterations of the cytoplasm. The latter contained deposits of bile pigment. Sometimes the cells were absent and replaced by granular debris, and the framework was collapsed. This process indicated transition from atrophy of the cells to necrobiosis and necrosis, usually referred to as central necrosis (fig 3). This was seen in 8 cases, in different degrees, while in 1 case the necrosis was peripheral.

Such degenerative changes as cloudy swelling or fatty degeneration were frequently noted. Fatty changes were observed in the liver in 10 cases, in 4 it was marked. The fatty infiltration was found to be chiefly central in 5 cases and peripheral in 1 and was diffusely distributed in 4.

Bile pigment in the liver cells was localized chiefly centrally (in 12 of 13 cases). In 8 cases it was marked, in 4 it was slight, while in 1 there was only a trace.

The Kupffer cells usually contained bile pigment; in 8 cases they were swollen. The Kupffer cells often assumed a tack shape, since they were slightly displaced but still connected with the cords of liver cells. This picture has been called capillary mobilization by Rossle¹¹.

The bile capillaries were dilated and the ramifications marked. In many places there was rupture of the bile capillaries, characterized by a funnel-shaped communication between the lumen of the bile capillary

11 Rossle, R. Entzündungen der Leber, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1930, vol. 5, pt. 1, p. 250.

and the pericapillary tissue (Disse) space. The wide opening of the funnel was directed toward the Disse space. The ruptures were especially prominent in the center of the lobules, whereas the dilatation was most marked in the periphery.

The bile ducts revealed mostly a narrowed lumen, probably due to compression by edematous periportal tissue. In only 1 case, in which

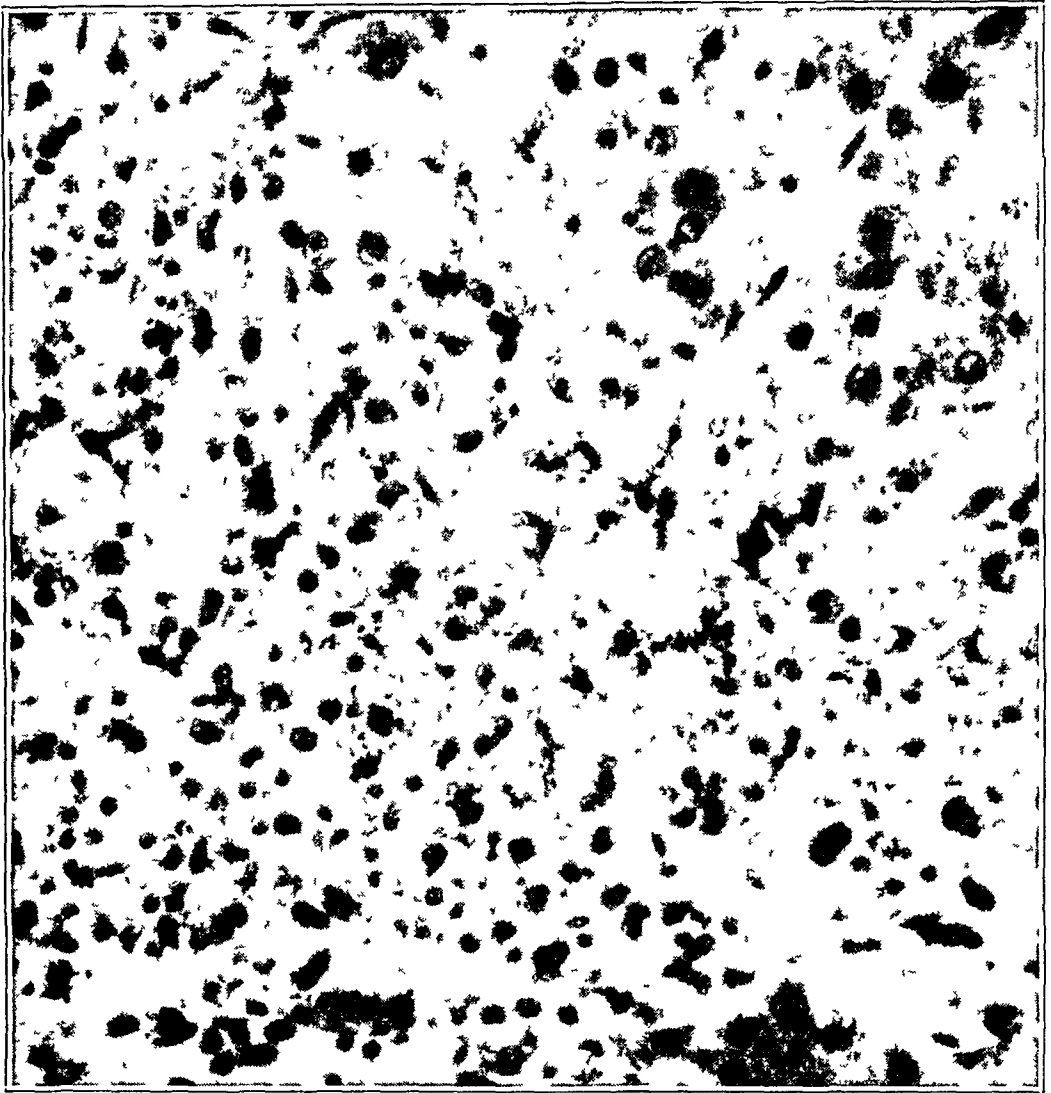


Fig 3—Intact swollen liver cells surrounding an area of central necrosis (high power)

there was a clinical history of two months' duration, were the ducts proliferated.

Infiltrations of the periportal septums in the form of round cells was marked in 4 cases, and slight in 7. In 4 cases the septums, in addition to the round cells, showed infiltration of polymorphonuclear leukocytes.

The reticulum fiber framework was usually intact, despite the marked dissociation of the cords of liver cells (fig 4 *A*). A striking picture was the widening of the network extending between the cords of liver cells

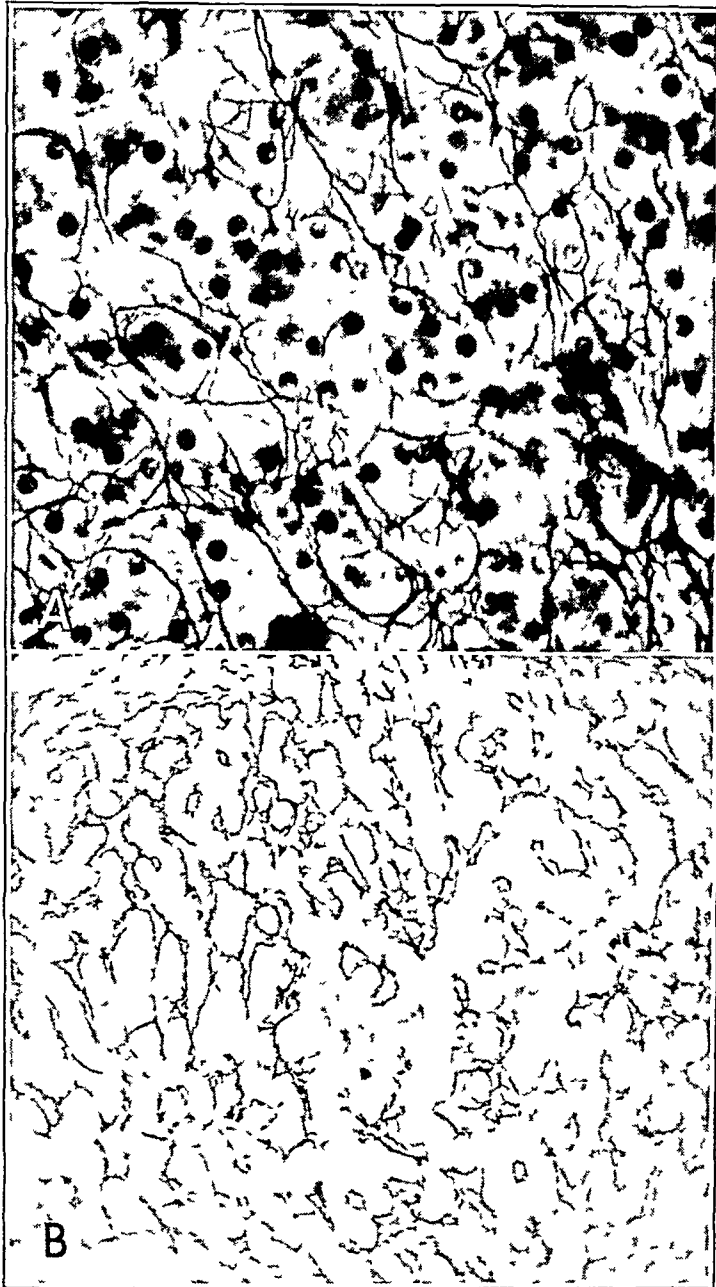


Fig 4—Sections specially stained to show reticulum *A*, reticulum fibers intact in spite of dissociation, *B*, interruption of fibers in the central area

and the blood capillaries, which indicated dilatation of the Disse spaces due to the edema. In some places, however, actual rupture of the framework was visible about the hepatic veins (fig 4 *B*)

The spleen was studied in 10 cases. In 4 there was increased fibrosis and in 7 marked congestion, in 6 of which there were focal aggregations of red blood cells, simulating hemorrhages.

The kidneys in 11 cases showed evidences of albuminuria, in 10 there were bile casts in the tubules and in 4 interstitial nephritis. Fatty degeneration and cloudy swelling of the tubules were characteristic, in 3 the changes were marked, while in 7 they were moderate. Proliferation of the glomerular endothelium was observed in 2 cases.

COMMENT

The condition in the cases described represents morphologically a type of fatal parenchymatous jaundice. In many of the cases the clinician had suggested the diagnosis of acute hepatitis. The onset of the disease with jaundice, progressive until death, indicates a primary disease of the liver. Striking is the acute fulminating course, although 2 patients lived longer than a month—two and three months, respectively—from the onset of the illness, but no signs of healing were observed histologically.

The clinical course suggested the diagnosis of acute yellow atrophy of the liver, with an infectious toxic cause, as indicated by fever, chills, pains in the joints and leukocytosis (up to 38,000 per cubic millimeter). A striking feature of differentiation, however, was the enlargement of the liver, which was even noted clinically and was the most prominent anatomic observation. In this respect one may compare our cases with the cases of nonfatal catarrhal jaundice in which the liver is also enlarged. In view of the clinical and anatomic observations, the condition in our cases may therefore be considered as an intermediary stage between catarrhal jaundice and acute atrophy of the liver.

This condition demonstrates that in fulminating parenchymatous jaundice the prognosis may be poor despite an enlarged liver. The study of our cases not only is interesting from a clinical point of view, but may throw light on the still questionable morphologic picture of the enlarged liver in parenchymatous or catarrhal jaundice.

Two different processes were in the foreground. One was damage of the liver cells, characterized by central necroses and heavy infiltration with fat and bile pigment. The presence of bile pigment in liver cells can be considered as a sign of damage since normal liver cells repel the bile pigment immediately and only necrobiotic cells store it. Generalized damage to the liver cells may lead finally to acute atrophy, however, it does not explain the enlargement of the organ, for the liver cells do not increase in size or number.

The enlargement was due to the presence of a protein-rich fluid between the liver cells, or edema. The spaces between the blood capil-

laries and the cords of liver cells, the Disse spaces, were markedly widened and contained coagulated proteins. The presence of proteins indicated that the edema was due to capillary damage, with subsequent inability to retain the plasma proteins within the lumen of the capillaries. Proteins bind water, and when lymphatic drainage is insufficient to carry away the escaped proteins, edema results. When the amount of escaped proteins is high, the increasing fluid accumulates between the cords of liver cells and finally destroys their structure, leading to the dissociation of the cells. The picture of dissociation may be similar to postmortem changes in bodies examined several days after death. In our cases, however, examination was made within three to nineteen hours after death, with only 1 exception (three days). There was no obvious relation between the severity of the histologic changes and the interval between death and autopsy. Marked dissociation was present in a case in which examination was made three hours after death, while it was absent in another in which autopsy was done nineteen hours after death.

The degree of dissociation varied. The interruption of the cords of liver cells was evidently effected not by changes of the cells themselves but by extracellular processes, as indicated by the normal staining of the nuclei. The dissociation and the break-up in some cases was so far advanced that single segregated liver cells were washed away into the blood stream and could be seen within the lumen of the hepatic veins and even in the portal veins (fig 5). This observation, however, may be considered as insignificant, since it has been seen in other conditions. The same surprising picture was described in cases of acute allylformiate intoxication,³ the course of which showed the development from the toxic edema to the parenchymatous hepatitis. The framework need not be affected in the presence of dissociation, as shown by special stains (fig 4). One is, therefore, dealing with damage both to the cells and to the capillaries, in the form of serous hepatitis. The presence of edema fluid rich in proteins between the capillaries and the parenchyma cells causes undernutrition and suffocation of the cells, since the diffusion of metabolic substances and oxygen from the capillaries to the cells is impaired. The cellular damage is responsible for the atrophy of the organ, while the capillary damage explains the enlargement of the liver.

As to the etiologic factor, we are unable to make a positive statement, but a toxin may be assumed. Sometimes a food poison was mentioned in the history, with gastrointestinal symptoms at the onset of the illness. Interesting is the history of the child in our group. Three other children of the same family also acquired jaundice at the same time that the patient was admitted to the hospital, but they recovered, while the patient died seven days after the onset of the illness. From the blood and feces

paratyphoid B bacilli were isolated, and the clinical course did not differ from that seen in the adults of our series. Probably a food poisoning can be suggested as the cause. The children that survived showed a picture similar to what has been described as the epidemic form of catarrhal jaundice.



Fig 5—Large numbers of liver cells in the lumen of a large branch of the portal vein in the presence of dissociation

Other factors, such as syphilis, gonorrhea and infections of the upper respiratory tract, were mentioned in our series. Probably several factors work together in the production of toxic hepatitis, similar to the conditions in catarrhal jaundice.

As to the pathogenesis of icterus, we believe that the combined damage to the capillaries and to liver cells is of importance. Damage

to the liver cells in central necrosis or marked dissociation is responsible for the interruption of the bile capillaries. The break-up of the wall of the capillaries formed by liver cells causes a communication between the bile capillaries and the Disse spaces. Bile escapes into the spaces, which are drained by the lymphatics, and regurgitates through the jugular vein into the general circulation. But in cases in which central necrosis alone is found, no jaundice may be present, as observed in many toxicoses, anemias and even congestion of the liver. On the other hand, simple serous hepatitis alone with widening of the Disse spaces does not cause jaundice. The severest form of serous hepatitis is the condition of the liver in beriberi, and jaundice is not observed with this disease. If merely localized necrosis occurs and the function of the remaining liver cells is intact the regurgitated bile is quickly excreted. However, when the localized central necrosis is combined with diffuse serous hepatitis the excretion of the regurgitated bile is impaired and the bilirubin level of the blood increases. Therefore, a combination of serous hepatitis and damage to the liver cells is the chief factor for the development of the jaundice, and this explanation probably holds for all types of parenchymatous diseases of the liver.

Regeneration of the liver in this condition may be possible in view of the fact that usually the framework of connective tissue is intact and therefore restitution of the cords of liver cells is possible. On the other hand, the existence of this fatal transitional form emphasizes the need for thorough and active therapy in every case of catarrhal jaundice. Therapy directed toward the damaged liver cells is difficult, but the abolishment of the edema may be more easily effected by intravenous injections of hypertonic solution of dextrose. These seem to be of greatest value, since they facilitate dehydration of the interstitial tissues and storage of glycogen.

SUMMARY

Fifteen cases of acute hepatitis are described. The fulminating fatal form appears to be an intermediary stage between catarrhal jaundice and acute yellow atrophy of the liver. The liver in each case was enlarged and characterized morphologically chiefly by damage to the epithelial cells and serous hepatitis, with dissociation of the liver cells. The clinical diagnosis was usually considered as primary hepatitis.

The dissociation of the cords of liver cells may be the result of severe serous hepatitis consequent to damage of the blood capillaries of the liver.

Icterus in parenchymatous jaundice is due to the combination of localized necrosis of the liver cells, or destruction of the cords, and general impairment of the function of the liver cells (serous hepatitis).

The enlargement of the liver in our cases and in cases of catarrhal jaundice is due to toxic edema.

FORMATION OF EDEMA IN THE EYELIDS OF MAN

INFLUENCE OF LOCAL TISSUE PRESSURE, SKIN DISTENSIBILITY,
LYMPH FLOW, INTRAORBITAL PRESSURE GRADIENT
AND VENOUS PRESSURE

GEORGE E BURCH, MD
NEW ORLEANS

The medical literature is particularly lacking in studies of the formation of edema in the eyelids of man, a subject of much clinical interest, especially in acute hemorrhagic nephritis, in which edema of the eyelids often precedes clinical evidence of edema elsewhere. The reasons for the uneven distribution of edema in this condition have only been conjectured. Fishberg¹ and Landis² mentioned the looseness of the tissues of the lids as a possible significant factor responsible, at least in part, for the early presence of edema in that area. They pointed out, however, that other important factors must exist, since in patients with acute hemorrhagic nephritis edema is not likely to develop in other areas of the body where the tissues are loose, such as the abdominal wall of a multipara. Peters³ stated that "tissue tension, if this is defined loosely as the pressure which resists deformation or distention, must also vary with anatomical structure. This is probably the factor which determines the uneven distribution of edema." Beach,⁴ in a discussion of edema of the eyelids, listed many causes of edema in that location, but failed to present any detailed mechanisms for accumulation of the fluid. The current textbooks of ophthalmology have likewise failed to present any adequate discussions of the mechanisms of formation of edema in the eyelids. Loeb,⁵ in an extensive review of the literature on edema, included nothing of particular significance concerning edema of the eyelids.

From the Department of Medicine, Tulane University of Louisiana School of Medicine, and the Charity Hospital

1 Fishberg, A. M. Hypertension and Nephritis, ed 3, Philadelphia, Lea & Febiger, 1934, p 114

2 Landis, E. M. Capillary Pressure and Capillary Permeability, *Physiol Rev* **14** 404, 1934

3 Peters, J. P. Body Water. The Exchange of Fluids in Man, Springfield, Ill, Charles C Thomas, Publisher, 1935, p 52

4 Beach, S. J. Edema of the Eyelids, *J A M A* **83** 17 (July 5) 1924

5 Loeb, L. Edema, *Medicine* **2** 171, 1923

This study is an attempt to evaluate some of the factors peculiar to the eyelid that might influence the interchange of fluid between the blood vessels and the tissue spaces within the lid

METHODS AND MATERIALS

These studies were conducted on 88 living persons, including 57 normal subjects and 31 subjects with various types of edema of the eyelids. The subjects varied in age from 8 to 84 years and included males and females of both the white and the Negro race

TABLE 1—*Tissue Pressure in Millimeters of Water for the Eyelids in 15 Normal Subjects**

Case No	Age	Sex	Race†	Right Lower Lid			Left Lower Lid		
				Eyes Open		Eyes Loosely Closed Supine	Eyes Open		Eyes Loosely Closed Supine
				Supine	Sitting		Supine	Sitting	
1	17	M	N	30	32	24			
2	59	F	N	24	28				
3	29	M	W	20			30	28	28
4	18	M	W				30	32	40
5	27	F	N	20	18	18			
6	18	M	N	32	30	32			
7	31	M	W	32	38	40			
8	28	M	W	20	22	20			
9	36	M	W				20	22	22
10	33	M	W				18	20	16
11	64	M	W	30			28		
12	29	M	W	18			20		
13	25	M	W	22			16		
14	27	M	W	20			21		
15	48	M	W	22			28		
Mean				24.2	28.0	26.8	23.4	25.5	26.5
Maximum				32	38	40	30	32	40
Minimum				18	18	18	16	20	16

* For the 21 lower lids analyzed collectively, the mean = 23.4 ± 0.7 mm. of water, the standard deviation, 5.1 ± 0.5 mm. of water, and the coefficient of variation, 21.67 ± 2.51 per cent. For the 9 lower lids loosely closed, considered collectively, the mean = 26.6 mm. of water. For the 10 lower lids considered collectively, with the subject in the sitting position, the mean = 27.0 mm. of water.

† In this table and in the accompanying tables, N indicates the Negro and W the white race.

Subcutaneous Tissue Pressure—With the use of the method previously described,⁶ determinations of subcutaneous tissue pressure were made in the lower lids of 15 normal subjects (13 males and 2 females), varying in age from 17 to 59 years. The patients rested quietly in the supine position, and values were obtained with the eyes open and closed loosely as in sleep. The subjects then assumed the sitting position, and determinations were again made with the eyes open. The number of determinations for each lid can be seen in table 1. In 2 normal female subjects, 35 and 50 years of age, the tissue pressure was determined in the evening before they retired and in the morning on awakening. All subjects were instructed not to move the eyeballs and lids during the determinations.

6 Burch, G. E., and Sodeman, W. A. The Estimation of the Subcutaneous Tissue Pressure by a Direct Method, *J. Clin. Investigation* **16**: 845, 1937.

The effect of the amount of interstitial fluid on subcutaneous tissue pressure was studied in 25 subjects, varying from 17 to 60 years of age. This effect was studied as follows. The adapter, manometer and pressure control unit of the tissue pressure apparatus were connected with one female portion of a three way stopcock, a 10 cc tuberculin syringe was connected with the other female portion and the tissue pressure needle to the third, or male, portion. Sterile physiologic solution of sodium chloride was drawn into the three way stopcock, and the valve was so manipulated that the solution filled the syringe and ran halfway up the adapter. Particular care was taken to remove all bubbles of air from the system. With the subject relaxed in the supine position, the needle was then inserted into the tissues to be studied and the valve of the three way stopcock so adjusted that the tissue pressure could be determined in the usual manner. The valve was readjusted, and 0.1 cc of the solution of sodium chloride was injected into the subcutaneous tissues. After the valve was reset another measurement of tissue pressure was made. This process was repeated after each 0.1 cc of solution was injected until the entire 1.0 cc had been expelled into the subcutaneous tissues. Observations were carried out for the lower lid, the face (area on the level with and about 2.5 cm anterior to the tragus of the ear), the volar surface of the forearm, the pretibial area, the prepuce of the males and the loose abdominal wall and the breasts of the nonpregnant multiparas. In the first 10 subjects as many of these areas were studied as the sex would permit. Additional subjects were studied until a sufficient number of observations for each area were obtained for analysis. Since the face was not studied simultaneously with the other areas and since the subjects previously used were not available, 7 different subjects were employed for the observations on the face.

Measurements of subcutaneous tissue pressure were made in edematous eyelids of 31 patients, the edema being due to various states (congestive heart failure, 8 patients, acute hemorrhagic nephritis, 2, mediastinal obstruction, 3, low amount of serum proteins, 2, myxedema, 1, infection, 1, senile changes, 10, undetermined cause, 4). All patients were in the supine position when the measurements were made. Repeated determinations were obtained on some subjects during the course of the edema.

Skin Distensibility—Determinations of skin distensibility were obtained by the method previously described.⁷ Certain changes in the apparatus were necessary for its application to the eyelid. A smaller caliper was made which offered a force of approximately 20 Gm, the bakelite cubes were made smaller so that the width of the "strip" of skin stretched measured 4 mm, and the brass bar for holding the cubes in place for sealing was modified so that the length of the "strip" was approximately 2 cm. The caliper was calibrated, and its calibration curve (fig 1) was found to have the formula,

$$\text{distance stretched (mm)} = -1.25 \text{ force (Gm)} + 51.2$$

Determinations of skin distensibility were made on both lower lids and on one forearm of 10 normal subjects, varying from 22 to 53 years of age. These subjects included 9 white (7 male and 2 female) persons and 1 Negro male. In 6 of these subjects both sides of the face (area on the level with and about 2.5 cm anterior to the tragus of the ear) were also studied. The subjects were deliberately chosen with a view to obtaining on the lower lid a strip of skin 2 cm long which was not arched, thereby eliminating the possibility of an error on

7 Sodeman, W. A., and Burch, G. E. A Direct Method for the Estimation of Skin Distensibility with Its Application to the Study of Vascular States, *J. Clin. Investigation* 17:785, 1938.

straightening an arched portion of the skin. The persons under observation lay in the supine position with the head resting on the occipital region and the face toward the ceiling. For the determinations on the lower lids, the subjects held the eyes vertically rotated toward the eyebrows. This position of the eyes unfolded the lower eyelid. The bakelite cubes were then sealed with collodion to the skin of the inferior portion of the lids so that the "strip" of skin stretched was approximately 10 to 15 mm from the margin of the lid and almost parallel with it. During the stretching there was no movement at the margin of the lid. With the same small apparatus the distensibility was determined in the forearm in the manner previously described.⁷ Determinations of skin distensibility were also made in the lower lids of patients with edema in that region.

Linear Rate of Lymph Flow in the Superficial Lymphatics of the Skin—The linear rate of lymph flow in the superficial lymphatics of the skin was determined by the method of McMaster.⁸ In order that the volume of dye injected intra-

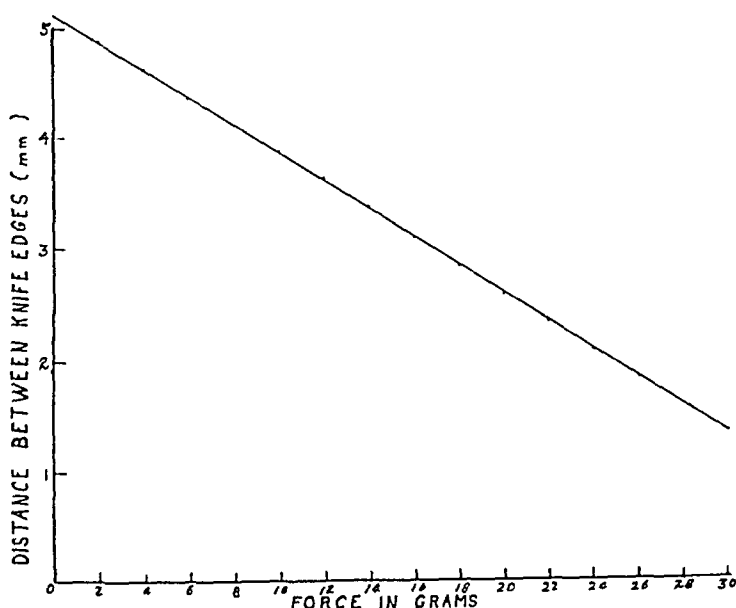


Fig 1—Calibration curve for the caliper used in determining the skin distensibility of the eyelid. The formula for the curve is Distance stretched (mm) = $-1.25 \text{ Force (Gm)} + 51.2$

dermally might be constant and accurate, a specially constructed apparatus, which has been described elsewhere,⁹ was employed for the injections. These observations were conducted on the lower eyelids of 9 normal subjects and of 1 subject with mild "senile edema"¹⁰ of the lower lids. All subjects were white men whose ages varied from 22 to 42 years. Eight subjects rested for fifteen minutes in the supine position and one lower lid of each patient was studied.

8 McMaster, P. D. Changes in the Cutaneous Lymphatics of Human Beings and in the Lymph Flow Under Normal and Pathological Conditions, *J. Exper. Med.* 65: 347, 1937.

9 Burch, G. E. A Simple Method for Accurate Injection of Small Volumes of Fluid, *Proc. Soc. Exper. Biol. & Med.* 40: 676, 1939.

10 The term "senile edema" as employed in this discussion refers to that type of puffiness of the lower eyelids which appears and progresses with senility.

The subjects then assumed the sitting position and the other lid was studied. The other 2 subjects rested for fifteen minutes in the sitting position and one lid of each was studied, they then assumed the supine position for study of the other lid. The temperature and relative humidity were constant (temperature, 75 F, relative humidity, 50 per cent) during these and all subsequent studies of the lymphatics. The lymphatics were observed as follows. Two hundredths of a cubic centimeter of patent blue V was injected intradermally, as described by McMaster, in the midline of the lid about 5 to 10 mm from the margin. Tracings of the visible lymphatics were made for record on sheets of cellulose acetate three, ten, twenty and thirty minutes after the injection. The tracings thus obtained were then analyzed in an effort to learn whether or not the upright and supine positions influenced the linear rate of lymph flow.

The effect of blinking on the linear rate of lymph flow in the superficial lymphatics was studied in the upper and lower eyelids of 11 subjects (9 normal persons and 2 with mild senile edema of the lower lids) whose ages varied from 23 to 74 years. The subjects remained seated, and the dye was injected in both lids of one eye, as previously described. After the injection blinking was restricted to a minimum and tracings of the superficial lymphatic vessels were made three, ten, twenty and thirty minutes after the injection. The other eye was similarly studied except that after the injection of the dye blinking was exaggerated. The tracings were analyzed in an attempt to learn whether or not blinking affected the linear rate of lymph flow.

Venous Pressure—Direct determinations of venous pressure were made in a vein of the lower lid of 2 white male subjects who were 65 and 74 years of age. Both subjects had mild senile edema of the lower lids. Values were obtained for the sitting and the supine position. The technic employed was that previously described,¹¹ except that an ordinary 27 gage needle without lateral openings was used. Only 2 subjects could be found who did not have an abnormal increase in venous pressure and who, at the same time, had sufficiently prominent and large veins in the lids to permit a direct determination of venous pressure with the use of a 27 gage needle.

Effect on the Volume of the Anterior Orbital Tissue of the Eye of Injections of Sterile Physiologic Solution of Sodium Chloride Into the Posterior Orbital Space in Dogs—Two dogs were anesthetized with ether after the area around both eyes had been shaved. Capsules of cellulose acetate similar to the capsule employed by Hooker¹² for indirect determinations of venous pressure were then sealed over the eyes with collodion, well away from the margin of the lid. A 22 gage spinal needle was then inserted through the top of the capsule, through the conjunctiva just medial to the eyeball and into the posterior orbital space. The point at which the needle penetrated the capsule was sealed with "lubriseal." The capsule was then connected by rubber tubing to a 10 cc pipet held horizontally, in which there was a small bead of xylene. Sterile physiologic solution of sodium chloride was injected very slowly through the spinal needle in amounts of 0.1 cc into the posterior orbital space until 1.0 cc had been injected. Resulting changes in volume of the tissues of the eye anteriorly after each injection of 0.1 cc were determined by movements of the bead of xylene in the pipet.

11 Burch, G. E., and Sodeman, W. A. A Direct Method for the Determination of Venous Pressure. Relationship of Tissue Pressure to Venous Pressure, *J. Clin. Investigation* **18** 31, 1939.

12 Hooker, D. R. Observations on the Venous Blood Pressure in Man, *Am. J. Physiol.* **35** 73, 1914.

RESULTS

Subcutaneous Tissue Pressure—The values obtained for subcutaneous tissue pressure in the eyelids of 15 normal subjects are summarized in table 1. The mean values for 12 right and 9 left lower lids with the eyes open and with the subject lying relaxed in the supine position were 24.2 and 23.4 mm of water, respectively. Since the difference of 0.8 mm is within the error for the technic employed, the values for the 21 lower lids were analyzed collectively. These pressures varied from 16 to 32 mm of water, with a mean of 23.4 ± 0.7 mm and a standard deviation of 5.1 ± 0.5 mm. The coefficient of variation was found to be 21.67 ± 2.51 per cent, a variation comparable to that of the weights of normal human livers¹³. Figure 2 graphically compares the values for tissue pressure of the lower eyelids with those previously reported⁶.

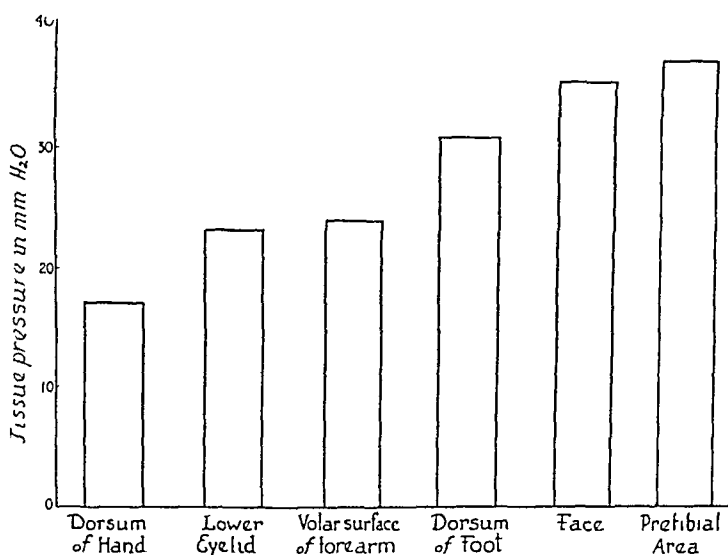


Fig. 2—Comparison of the mean subcutaneous tissue pressure in the lower lids with that of five other common sites of edema of normal persons

for the dorsum of the hand, the volar surface of the forearm, the dorsum of the foot and the pretibial area. The mean tissue pressure in 10 normal lower lids, determined with the subject in the sitting position, was 27.0 mm of water, a difference of 1.4 mm of water from that determined with the subject in the supine position. When statistical methods were used for the study of small samples¹⁴ this difference was found not to be significant. The mean of the variations of the values for the supine position from those for the sitting position was found to be 1.4 mm of water, with a standard error of ± 0.95 mm of water, twice the

13 Pearl, R. *Introduction to Medical Biometry and Statistics*, ed 2, Philadelphia, W. B. Saunders Company, 1930.

14 Mainland, D. *The Treatment of Clinical and Laboratory Data*, Edinburgh, Oliver & Boyd, 1938.

standard error being greater than the mean, 1.4 mm. In 9 normal subjects lying relaxed in the supine position with the lids closed loosely as in sleep, the mean subcutaneous tissue pressure was 26.6 mm of water. By the same method of statistical study the mean of the differences between the values with the eyes closed loosely and those with the eyes

TABLE 2—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Lower Lid*

Case No.	Age	Sex	Race	Volume of Injected Sterile Physiologic Solution of Sodium Chloride, Cc										
				0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
1	17	M	N	30	26	26	24	30	24	23	24	22	24	24
2	59	F	N	24	18	18	18	18	16	10	10	10	10	10
3	29	M	W	30	24	24	22	20	22	24	24	26	30	30
4	18	M	W	40	63	65	60	54	50	52	50	54	50	52
5	22	F	N	20	18	18	30	32	32	32	32	30	30	32
6	18	M	N	32	38	36	34	36	34	36	34	34	30	28
7	31	M	W	32	32	30	30	32	38	44	40	42	43	44
8	28	M	W	20	10	10	12	12	18	20	20	22	20	18
9	36	M	W	20	20	24	24	24	24	24	20	20	18	22
10	33	M	W	18	22	24	30	28	28	30	30	30	32	32
Mean				26.7	27.1	27.5	28.4	28.6	28.6	29.5	28.4	29.0	28.7	29.2
Maximum				40	62	65	60	54	50	52	50	54	50	52
Minimum				18	10	10	12	12	16	10	10	10	10	10

TABLE 3—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Volar Surface of Forearm*

Case No.	Age	Sex	Race	Volume of Injected Sterile Physiologic Solution of Sodium Chloride, Cc										
				0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
1	17	M	N	48	70	100	124	166	192	228	248	152	172	176
2	59	F	N	24	92	88	94	106	108	42	96	102	106	96
3	29	M	W	30	80	130	150	190	200	210	210	208	220	216
4	18	M	W	32	36	40	100	150	154	162	172	184	192	208
5	22	F	N	20	28	68	84	100	122	100	130	131	150	122
6	18	M	N	20	58	104	122	150	158	158	150	190	192	196
7	31	M	W	46	88	124	153	150	168	172	178	178	182	182
8	28	M	W	40	88	100	140	151	184	202	210	222	222	210
9	36	M	W	22	30	38	52	54	58	64	64	100	118	128
10	33	M	W	22	40	52	78	98	112	118	120	122	128	130
Mean				30.4	61.0	84.4	109.7	145.6	145.6	145.6	157.8	158.9	168.2	166.4
Maximum				48	92	130	153	190	200	228	248	222	220	210
Minimum				20	28	38	52	54	58	42	64	100	118	96

open was found to be 1.1 mm of water, with a standard error of ± 1.7 mm, thus indicating that the values with the eyes open and those with the eyes closed cannot be considered significantly different. In 2 normal subjects the values for tissue pressure in the left lower eyelids during the evening were 16 and 38 mm, and the following morning 18 and 38 mm of water respectively.

Tables 2 to 8 summarize the effects of the subcutaneous injection of 10 cc of physiologic solution of sodium chloride on the subcutaneous

TABLE 4—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Prepuce*

Case No	Age	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected Cc											
			0	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9	1 0	
1	17	N	36	56	50	50	54	62	54	40	44	40	42	
3	29	W	32	40	42	50	60	62	70	70	70	72	74	
4	18	W	34	42	32	84	90	110	88	90	90	100	104	
6	18	N	40	40	68	68	88	100	88	94	98	104	110	
7	31	W	30	34	32	34	36	40	40	42	40	40	40	
8	28	W	20	95	104	104	104	110	110	112	114	116	122	
9	36	W	18	36	42	44	46	44	44	44	46	48	46	
10	33	W	38	48	58	60	62	62	60	62	62	60	62	
Mean			31.0	49.0	56.0	61.8	67.5	73.8	69.3	69.3	70.5	72.5	75.0	
Maximum			40	95	104	104	104	110	110	112	114	116	110	
Minimum			18	34	32	34	46	40	40	40	40	40	42	

TABLE 5—*Relation of Tissue Pressure to Increase in Interstitial Volume in the Pretibial Area*

Case No	Age	Sex	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected Cc											
				0	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9	1 0	
2	59	F	N	48	48	84	88	104	112	122	148	166	166	170	
3	29	M	W	42	42	120	170	200	226	200	226	250	262	262	
4	18	M	W	28	140	144	222	184	218	212	242	264	210	222	
5	22	F	N	50	78	108	196	216	232	182	192	206	238	218	
6	18	M	N	30	90	144	182	190	204	220	270	290	304	306	
7	31	M	W	44	102	164	194	198	206	212	218	221	198	200	
8	23	M	W	42	122	200	210	246	130	162	186	204	212	218	
9	36	M	W	24	60	82	100	118	128	132	132	140	140	150	
10	28	M	W	28	60	84	108	120	126	132	138	144	150	158	
Mean				37.3	82.4	125.5	163.3	175.1	175.7	175.0	194.7	209.4	209.0	210.4	
Maximum				50	140	200	222	246	232	220	270	290	304	306	
Minimum				28	42	82	88	104	112	122	132	144	140	150	

TABLE 6—*Relation of Tissue Pressure to Increase in Interstitial Volume of the Breasts of Multiparas*

Case No	Age	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected Cc											
			0	01	02	03	04	05	06	07	08	09	10	
2	59	N	16	36	20	40	28	30	32	24	28	28	30	
16	26	N	22	30	32	48	58	58	56	64	72	74	74	
17	53	N	30	30	52	52	62	64	64	60	60	68	68	
18	46	N	32	40	44	44	50	50	50	48	48	48	48	
19	60	N	28	46	46	44	46	44	44	40	38	38	39	
20	29	N	30	70	76	76	76	80	86	88	88	92	96	
21	42	N	32	38	40	46	50	56	62	64	62	64	76	
22	39	N	28	42	60	80	84	88	88	92	92	90	92	
23	30	N	28	42	52	66	66	68	72	76	82	78	78	
Mean			27.3	41.6	46.9	55.1	57.8	59.8	61.6	61.8	63.3	64.4	66.8	
Maximum			32	70	76	76	76	88	88	92	92	92	96	
Minimum			16	30	20	40	28	30	32	24	28	28	30	

tissue pressure in the lower eyelid, volar surface of the forearm, prepuce, pretibial area, breast, abdomen and face of normal subjects. The results for the six areas are graphically illustrated by figure 3. It can be seen that the injection of the physiologic solution of sodium chloride into the subcutaneous tissues of the lower eyelids produced practically no change in the subcutaneous tissue pressure. The mean value of 26.7 mm. of

TABLE 7—*Relation of Tissue Pressure to Increase in Interstitial Volume of the Abdominal Wall of Multiparas*

Case No	Age	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected Cc											
			0	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9	1 0	
5	22	N	18	100	80	82	88	82	58	60	70	78	66	
16	26	N	18	20	20	32	44	44	50	54	52	52	38	
17	33	N	19	22	40	58	70	70	70	72	74	74	70	
18	46	N	16	32	38	68	70	68	68	68	70	78	80	
19	60	N	18	28	36	40	40	42	42	40	42	42	38	
20	29	N	38	58	110	128	142	110	118	112	104	110	112	
21	42	N	44	50	70	72	72	76	80	82	84	90	92	
22	30	N	40	42	58	68	70	78	82	84	86	90	92	
23	30	N	16	28	38	42	46	44	46	52	54	82	58	
Mean			25.2	42.2	54.4	65.6	71.6	68.2	68.2	69.3	70.7	77.3	74.0	
Maximum			44	100	110	128	142	110	118	112	104	110	112	
Minimum			16	20	20	32	40	42	42	40	42	42	38	

TABLE 8—*Relation of Tissue Pressure to Increase in Interstitial Volume of the Face*

Case No	Age	Sex	Race	Volume of Sterile Physiologic Solution of Sodium Chloride Injected, Cc											
				0	0 1	0 2	0 3	0 4	0 5	0 6	0 7	0 8	0 9	1 0	
23	30	F	N	38	108	180	202	214	216	234	242	244	252	256	
64	31	F	N	48	70	94	106	106	118	138	146	162	180	184	
65	29	F	N	36	100	148	206	160	180	204	246	272	282	306	
66	59	F	N	28	70	130	156	197	220	252	272	286	300	320	
67	17	F	N	38	68	91	110	136	158	160	178	196	202	208	
68	18	F	N	24	112	150	202	206	206	212	214	214	214	228	
69	30	F	N	39	110	184	210	262	278	313	333	346	358	366	
Mean				35.9	91.1	139.7	170.3	183.0	196.6	216.1	233.0	245.7	255.4	264.0	
Maximum				48	112	184	210	262	278	313	333	346	358	366	
Minimum				24	68	91	106	106	118	138	146	162	180	184	

water increased only to a mean of 29.2 mm. after the injection. The difference between these means was found not to be statistically significant. (Any statistical analysis of data in this paper for samples of less than 15 was performed by the methods previously mentioned,¹⁴ and for those of 15 or greater, by the methods described by Pearl¹³.) There was a definite increase in the values for tissue pressure in the five other areas. This increase was especially marked for the volar surface of the forearm, the face and the pretibial area. In the first site the values rose from a mean of 30.4 mm. of water before the subcutaneous injection

of fluid to a mean of 166.4 mm of water after the injection, in the face and the pretibial area the rise was even greater, increasing from a mean of 37.3 and 35.9 mm of water respectively, before the solution of sodium chloride was injected, to 210.4 and 264.0 mm after the injection. The rises in the tissue pressure produced by the cubic centimeter of solution of sodium chloride injected into the subcutaneous tissues of the breast, the abdominal wall and the prepuce were found to be statistically significant. In these three areas the elevations in the tissue pres-

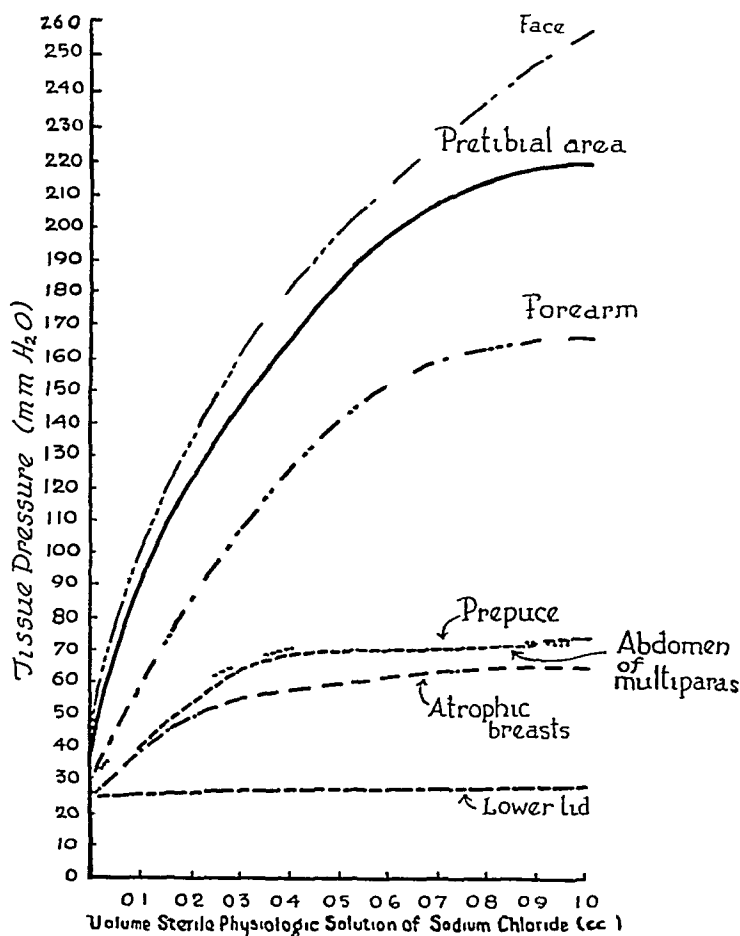


Fig 3—Effect of subcutaneous injections of 10 cc of physiologic solution of sodium chloride on the subcutaneous tissue pressure in seven common sites of edema, the breasts and abdominal wall being those of nonpregnant multiparas

sure were essentially equal. It was also noted that the injected solution of sodium chloride tended to diffuse with greater ease throughout the subcutaneous tissues of the lower lid than in the other areas, and with least ease in the forearm, the pretibial area and the face, although the local area of swelling produced by the injection appeared to be larger in the eyelids than in the other areas studied.

The values for subcutaneous tissue pressure in the patients with edema of the eyelids are summarized in table 9. It can be seen that

TABLE 9—Tissue Pressure Values, in Millimeters of Water, for 31 Patients with Edema of the Eyelids and Other Areas

Case No	Cause of Edema	Age	Sex	Race	Right Lower Lid	Left Lower Lid	Upper Lid as Indicated	Other Areas as Indicated	Comment
24	Undetermined	52	F	W	36	36			Edema of one year's duration
25	Congestive heart failure	26	M	N	44			Prepuce 138	Edema of lid mild edema of prepuce marked
26	Undetermined	43	F	N	40	42			Moderate amount of edema
27	Myxedema	26	F	W	24	62			9/23/34 Moderate amount of swelling
28	Mediastinal obstruction	52	F	N	44	40	Right 46 Left 42		11/4/38 Decreasing edema
29	Exophthalmic goiter	29	F	N	48	58			Edema marked on right side moderate on left
30	Senility	74	M	W	44	48			Cause of edema?
31	Senility	65	M	W	40	40			Moderate edema
32	Malaria and hypoproteinemia	14	M	W	32	42		Right forearm 44	Moderate edema
33	Senility	70	M	N	40				9/1/38 Marked edema of lid clinically no edema of arm
34	Congestive heart failure	37	M	N	40				9/9/38 No edema
35	Syphilis of central nervous system	38	M	N	32			Prepuce 88	Mild edema
36	Congestive heart failure	55	M	N	28		Right 82		Marked edema no edema of lids
37	Congestive heart failure	84	M	N	38		Right 38 Left 40		Cause of edema?
38	Infection	40	M	N	48	38		Prethibial 60 Prethibial 84	Relatively much more edema of lids
39	Senile changes (?)	38	M	W	28		Right 36 Left 42		Edema in both areas
40	Senility	70	M	W	42				Left lid was affected and edematous
41	Mediastinal obstruction	59	F	N	24	22			right lid unaffected
42	Congestive heart failure and chronic hemorrhagic nephritis	10	M	N	30	28			Mild senile type of edema
43	Senility	63	M	W	44	33			Marked edema in left lid, mild in right
44	Acute hemorrhagic nephritis	8	M	N	36	38			Moderate edema of both lids on right side and little in lower left lid
45	Senility	70	M	W	24	22			Moderate in both lids
46	Undetermined	12	F	N	78	44		Forearm 42	Moderate edema, very loose lids
47	Senility	48	M	W	24	42			10/17/38 Mild edema, 4 30 p m
48	Senility	64	M	W	20	16			10/18/38 Marked edema, 9 a m
49	Senility	51	M	W	16	16			10/24/38 No edema
50	Congestive heart failure	40	F	N	34	26		Forearm 20	Moderate edema of both lids
51	Mediastinal obstruction	58	M	W	40	36			Marked edema of lids and none of forearm
52	Congestive heart failure	56	F	N	24	24			Mild edema in right lid and moderate in left lid
53	Hypoproteinemia	20	F	W	58				Mild edema infection also in right lid
70	Acute hemorrhagic nephritis	50	F	N	18	12		Forearm 71 Right forearm 30 Left forearm 30	Mild edema

regardless of the cause of the edema the tissue pressure did not increase to high values. In only 4 instances did it surpass 54 mm of water, the maximum normal value found for the pretibial area, for which values tend to be consistently high. The maximum value found in any of the eyelids with edema was 78 mm.

Skin Distensibility—The results obtained for the distensibility of the skin of the lower eyelid, face and volar surface of the forearm in the normal subject are shown in table 10. A difference in the distensibility of 0.18 mm of stretch per centimeter of skin per 20 Gm of force was found between the right and the left lower lid. The standard error of this difference was ± 0.21 , thus showing that the difference for that group

TABLE 10—*Distensibility in the Lower Eyelids and in the Volar Surface of the Forearm in 10 Normal Subjects (Units of Distensibility Expressed in Millimeters of Stretch Per Centimeter of Skin Per 20 Gm of Force)**

Case No	Age	Sex	Race	Right Lid	Left Lid	Right Side of Face	Left Side of Face	Volar Surface of Forearm
54	29	F	W	0.92	1.26	0.88	0.70	0.46
55	22	F	W	0.92	1.36	0.90	0.84	0.52
56	40	M	W	1.38	1.02	0.62	0.76	0.32
57	37	M	W	0.80	0.84	0.62	0.64	0.36
58	27	M	N	1.64	1.38	0.81	1.02	0.38
59	28	M	W	0.60	0.56			0.28
60	36	M	W	1.44	1.06			0.86
61	48	M	W	2.18	1.34			0.54
62	50	M	W	0.98	1.06			0.42
63	53	M	W	2.26	1.46	0.40	0.24	0.62
Mean				1.31	1.13	0.71	0.70	0.48
Maximum				2.26	1.46	0.90	1.02	0.86
Minimum				0.60	0.56	0.40	0.24	0.28

* For the 20 lids analyzed collectively, the mean distensibility = 1.23 ± 0.06 mm the standard deviation, 0.43 ± 0.04 mm, and the coefficient of variation, 34.73 ± 4.01 per cent.

was not significant. Therefore, the data for the 20 lower eyelids of the 10 normal subjects were analyzed collectively. The mean for the 20 lids was 1.23 ± 0.06 mm of stretch per centimeter of skin per 20 gm of force, with the minimum and maximum values 0.56 and 2.26 mm, respectively. The standard deviation was 0.43 ± 0.05 mm and the coefficient of variation 34.73 ± 4.01 per cent. It can be seen from the table that the skin of the lower lid is approximately two and a half times as distensible as that of the volar surface of the forearm and twice that of the face. It was previously found⁷ that the distensibility of the skin of the volar surface of the forearm was about three times that of the pretibial area, twice that of the dorsum of the foot, three-fourths that of the dorsum of the hand, and one-half that of the abdomen. These results indicate quantitatively that the distensibility of the skin of the lower eyelid is greater than that of the other regions mentioned, being

closely approached only by that of the skin of the abdomen. This relative difference is graphically illustrated by figure 4, in which the distensibility of the skin of the forearm was arbitrarily expressed as 100. Obviously, actual values could not be graphed, since the width and length of skin, as well as force, used in these studies on the eyelid differed from those used in previously reported studies on the pretibial area, the dorsum of the hand and foot and the abdomen. However, since the skin of the forearm was studied under both conditions, it was used as the standard for reference in the construction of the figure.

Linear Rate of Lymph Flow in the Superficial Lymphatics—In the 10 white male subjects studied by the McMaster method, the linear rate of lymph flow in the lower eyelid was invariably more rapid in the

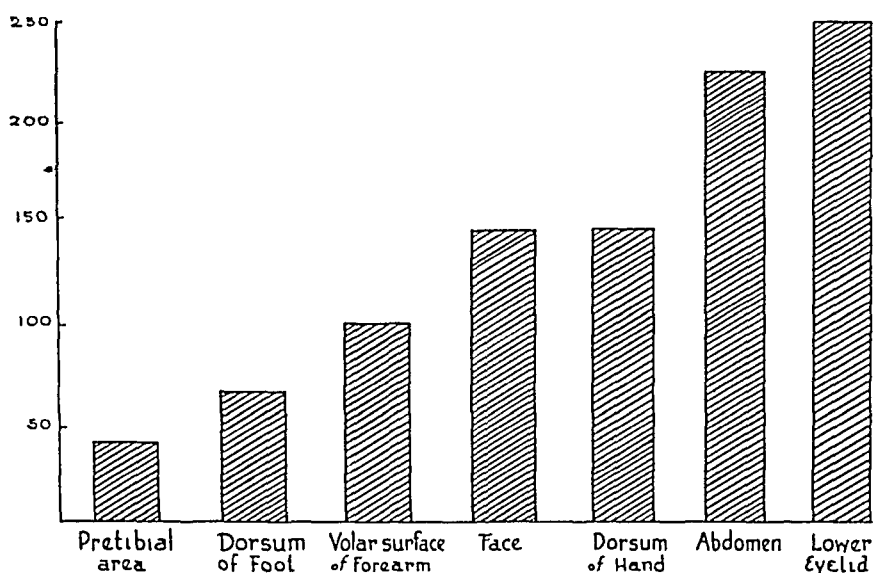


Fig. 4—Comparison of the values for skin distensibility of seven areas of the body of normal subjects. The figure was constructed on the basis of the distensibility of the skin of the volar surface of the forearm, which was arbitrarily considered to be 100.

sitting than in the supine position. Tracings from a typical subject are shown in figure 5. Not only was the rate of flow more rapid in comparable vessels in the sitting than in the supine position but, in many instances, there was an increase in the number of vessels filled. These findings are in agreement with those of McMaster, who observed similar positional effects on the lymph flow in the superficial lymphatics of the forearm. It was also noted that the rate of diffusion of the dye in the original wheal at the site of injection in some instances tended to be more rapid in the skin and subcutaneous tissues of the lid than that described for the forearm by McMaster. This difference was also noted in the forearms of subsequent subjects studied during other observations. In the 2 subjects with senile edema of the lower lids the linear rate of

lymph flow was also greater with the subject in the sitting than in the supine position. The results of studies on the 2 subjects in whom the observations were made first in the sitting and then in the supine position did not differ discernibly from those on the other 8 subjects in whom the order of observation was reversed.

In the 11 white male subjects (9 normal and 2 with senile edema of the lower eyelids) it was found that, except in the upper eyelids of the 2 normal subjects, the linear rate of lymph flow was much more rapid with blinking of the lids. This is illustrated by a typical case shown in figure 6. These results are in agreement with those of McMaster, who found that exercise increased the linear rate of lymph flow in the superficial lymphatics of the forearm. In the 2 exceptions there was no appar-

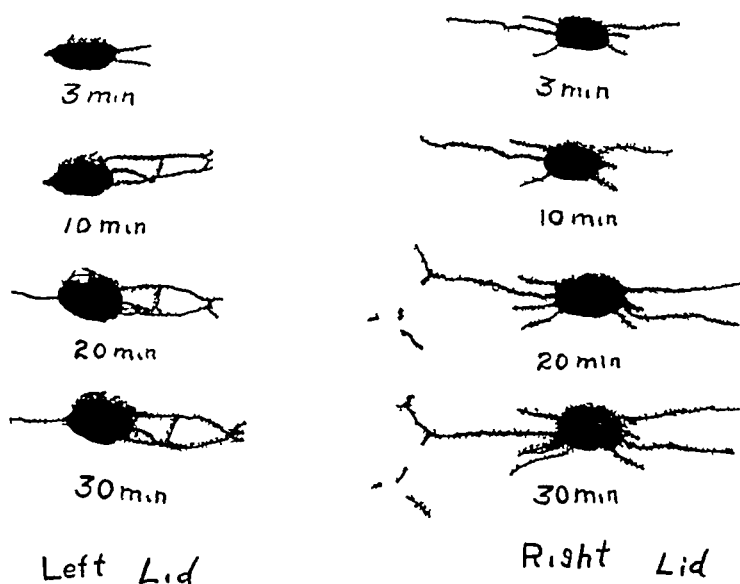


Fig 5—Effect of position of the subject on the linear rate of lymph flow in the superficial lymphatics in the lower eyelids of a typical subject, the tracings of the lymphatics being made three, ten, twenty and thirty minutes after the intra-dermal injection of patent blue V. Observations on the left lid were made with the subject in the supine position and those on the right with the subject sitting. The vessels draining nasally are to the left.

ent difference in the rate of flow in the upper lids with and without the influence of blinking, in the other subjects the temporal direction of flow was more rapid with blinking, while the nasal direction of flow was more rapid without blinking. A satisfactory explanation for these differences cannot be advanced at present. They may be due to the fact that the drainage was into the deeper tier of lymphatics, which anastomose with the superficial lymphatics,¹⁵ thereby precluding the observation of the

15 Most, A. Ueber die Lymphgefäße und die regionären Lymphdrüsen der Bindehaut und der Lider des Auges, Arch f Anat u Physiol, 1905, pp 96-110.

flow. Blinking produced more rapid diffusion of the dye from the lymph vessels as well as more rapid spread of the dye from the original site of injection. No discernible difference in the results could be found between the 2 subjects with senile edema of the lower lids and the 9 normal subjects.

Venous Pressure—In the 2 subjects who had veins of the lower lid sufficiently large for direct measurements of venous pressure, the venous pressures were found to be 10.6 and 12.4 cm. of water respectively, in the supine position and 4.8 and 2.2 cm. in the sitting position. Both of these patients suffered from senile edema of the lower eyelids, but were free from any evidence of venous obstruction.

Effect on the Volume of the Anterior Orbital Area of Injecting Physiologic Solution of Sodium Chloride into the Posterior Orbital

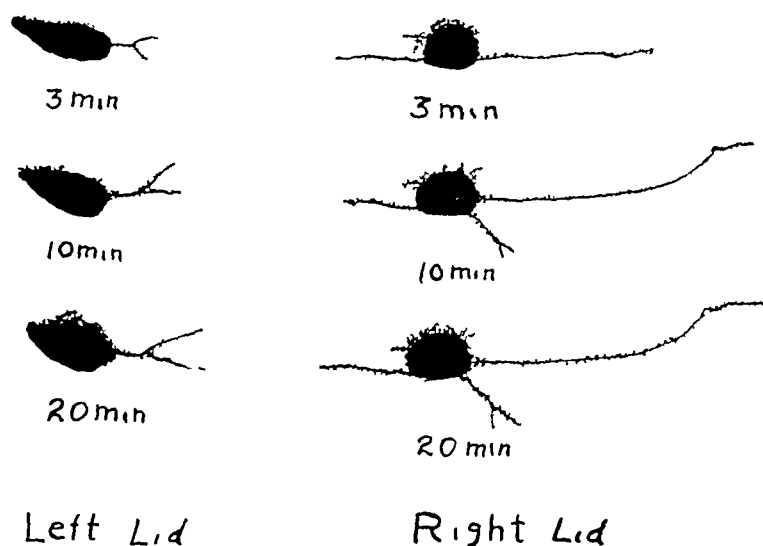


Fig. 6—Effect of blinking on the linear rate of lymph flow in the superficial lymphatics in the lower eyelids of a typical subject, the tracings being made three, ten and twenty minutes after intradermal injection of patent blue V. Observations on the left lid were made with blinking maintained at a minimum and on the right with blinking exaggerated. The vessels draining nasally are to the left.

Space—The changes in volume noted for the anterior orbital structures of both eyes of 2 dogs during the injection of 10 cc. of physiologic solution of sodium chloride into the posterior orbital space are summarized in figure 7 A, B, C and D. With the injection of the solution of sodium chloride there was a concomitant change in the volume of the tissues anteriorly, that is, the eyelids, and probably the eyeball, were pushed outward. The lids could be seen to become more prominent. It could not be determined by inspection whether this increase in prominence of the lids was due to deep structures pushing the lids anteriorly or whether there was an actual accumulation of fluid in the lids. There

was a lag, however, between the completion of each injection and the occurrence of the maximum change in volume of the structures anteriorly This lag will be discussed more fully later

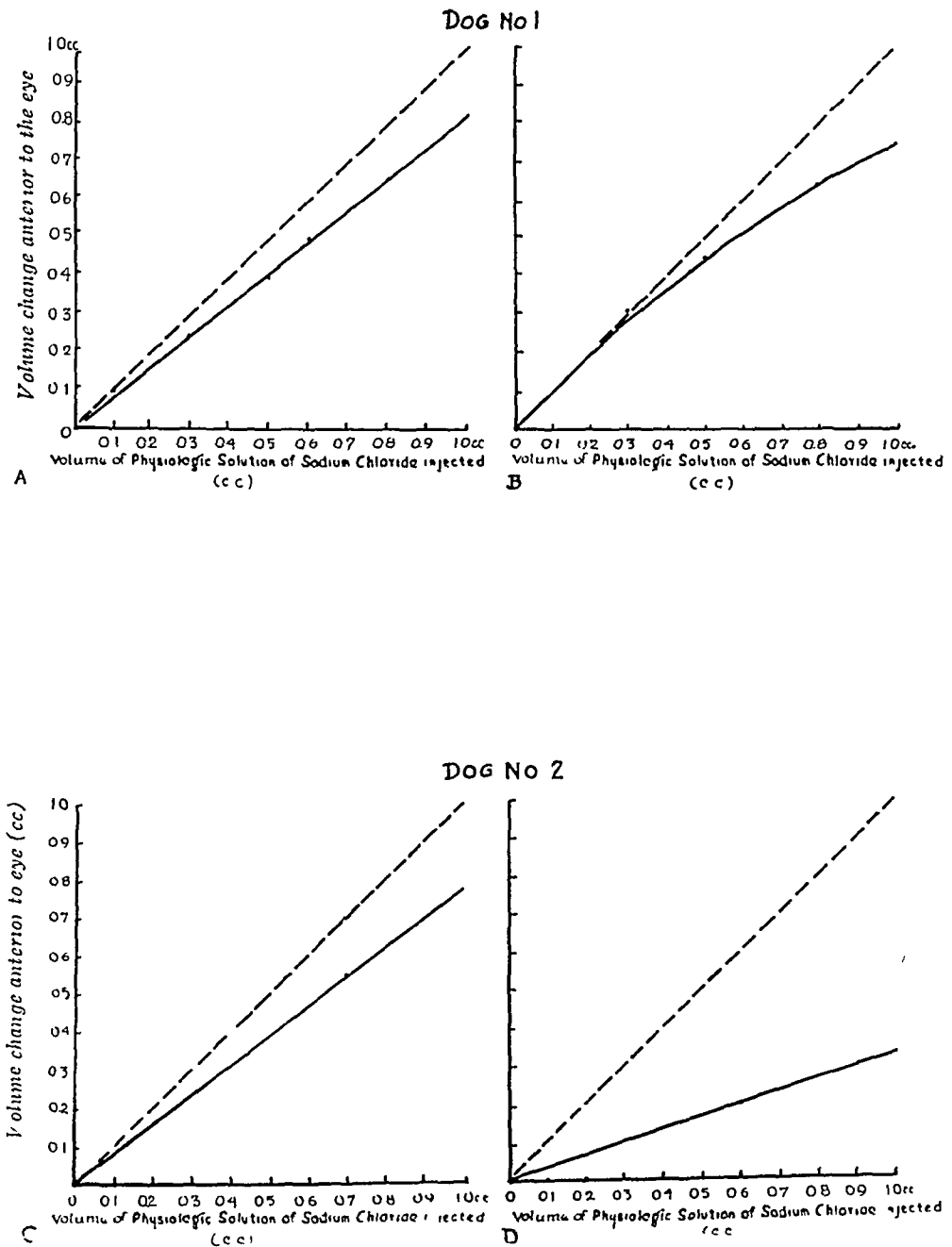


Fig 7—Effect of injection of 10 cc of physiologic solution of sodium chloride in the posterior orbital space on the volume of the anterior orbital structures of 2 dogs A and D show the results for the left eyes of the respective dogs, and B and C, for the right eyes The interrupted line illustrates the curve that would result were the changes in volume of the anterior structures equal to the volume of the solution of sodium chloride injected in the posterior orbital area The continuous line illustrates the actual results

COMMENT

A mean subcutaneous tissue pressure for the lower eyelids of 23.4 mm of water, a value almost equal to the mean pressure of 23.6 mm previously found⁶ for the forearm, would at first prompt one to consider the looseness of the tissues of the eyelids of little significance in facilitating the accumulation of interstitial fluid in the lids. Surely, from these findings alone, it would not seem that tissue tension influenced the volume of interstitial fluid any differently in the eyelids than in the forearm. However, when 1.0 cc of isotonic solution of sodium chloride was injected into the subcutaneous tissues of the volar surface of the forearm, a relatively great rise in tissue pressure occurred, while a similar injection into the subcutaneous tissues of the lower lid produced almost no change in tissue pressure. An increase of 0.1 cc in the volume of the local subcutaneous tissue produced a greater rise in subcutaneous tissue pressure in the forearm, as well as in all other areas studied, than a change of volume ten times as great produced in the eyelid. It appears from these findings that the differences in the values for tissue pressure are not due entirely to differences in diffusion of the injected fluid, but in a large part to variations in distensibility of the respective tissues. Furthermore, in the presence of edema, which was marked in some instances, the subcutaneous tissue pressure of the eyelids was found to be relatively little increased regardless of the stage of the edema (table 9). On the other hand, in some instances, tissue pressure was found to rise markedly in the forearm in the presence of relatively less, but progressing, edema. Subjects 9 and 30 (table 9), who were suffering from hypoproteinemia, a condition tending to produce edema with equal force throughout the body, had edema of the eyelids and not of the forearm. At the same time, in both subjects the subcutaneous tissue pressure in the eyelids, in spite of the local edema, was less than that in the non-edematous forearm. Essentially the same sort of relationship as that observed between the eyelid and the forearm was also found in other areas studied, namely, the loose pendulous breasts and loose abdominal wall of multiparas, the prepuce and the pretibial area. In the first three areas the difference was not as marked, but nevertheless it was sufficient to be significant. It has also been noted¹⁶ that in cases of scleroderma, a condition in which the subcutaneous tissues are dense and atrophic, the antithesis to the state of the tissues of the normal eyelids, the tissue pressure is greater than in a similar uninvolved area, likewise, the development of edema produced a marked increase in the tissue pressure. These

16 Sodeman, W. A., and Burch, G. E. (a) The Tissue Pressure in Subcutaneous Edema, *Am J M Sc* **194** 846, 1937, (b) Tissue Pressure: An Objective Method of Following Skin Changes in Scleroderma, *Am Heart J* **17**: 21, 1939.

data tend to indicate that the looseness of the tissues of the eyelids renders them distensible, so much so that they are unable to benefit much from the limiting influence of tissue pressure on the formation of edema. It is probable, however, that with very marked edema and considerable distention of the lids, tissue pressure may become a significant factor in limiting the formation of edema. Therefore, on the basis of tissue pressure alone, in the presence of any state that would tend to favor an equal accumulation of tissue fluid throughout the body, the eyelids would be less capable of preventing or limiting the accumulation of fluid and would be expected to become edematous early. Since tissue pressure in the lids was not found to vary with the position, the time of day or the position of the lids, that is, whether they were open or loosely closed, as in sleep, one would not expect the interstitial fluid of the lids to vary under those circumstances as a result of tissue pressure. This is particularly significant, as will be discussed later, in the explanation of the tendency for edema of the lids to develop during sleep when the subject is in the supine position and to disappear when the patient is up and about.

The studies of distensibility ("stretchability") of the skin of the lower eyelids of normal subjects showed it to be greater than that of any other common site of edema studied, even than that of the abdominal wall. As stated previously,⁷ the skin acts as an important factor in limiting tissue pressure and, in turn, edema formation. The extreme distensibility of the skin of the eyelids apparently has relatively little effect on the underlying subcutaneous tissue pressure, at least until large amounts of interstitial fluid have accumulated. This was evidenced by the failure of the tissue pressure to rise when fluid was injected subcutaneously and by the relatively small elevation in patients with edema of the lids. It appears, therefore, that, all things being equal, on the basis of distensibility of the skin, edema would tend to develop more readily in the eyelids than in the pretibial area, the dorsum of the hand and foot, the forearm, the face and probably the abdominal wall. In nonpregnant multiparas the values for distensibility of the skin of the abdominal wall and of the eyelids approximate each other so closely that it is impossible to be certain that distensibility of the skin influences formation of edema any differently in the two areas.

The studies of the linear rate of lymph flow in the superficial lymphatics of the eyelids showed it to be greater with the subject in the upright than in the supine position. This was evidenced by an increase in the linear rate of flow in similar vessels as well as by an increase in the number of vessels visualized, and tends to show that when the effects of gravity favor the return of lymph to the venous circulation the rate of lymph flow is increased. Therefore, during the day, when a person is up and about and performing his daily duties, the drainage of lymph from the lids is more active than it is at night, when he is asleep and resting.

horizontally in bed. Although this gravitational effect on lymph flow may not abnormally influence the accumulation of interstitial fluid in the eyelids during sleep, it must facilitate rapid removal of such fluid during the day and must be significant in the presence of edema of the lids.

Since the linear rate of lymph flow in the superficial lymphatics is increased by movement, such as blinking, of the lids, it may be surmised that during sleep, when movement of the lids is at a minimum, lymph flow is not so rapid as during the day, when movement of the lids is relatively great. Sleep would, therefore, favor the accumulation of interstitial fluid, while movement of the lids during the day would favor its removal. On this basis, then, edema of the eyelids would be more likely to disappear during the day, when the person is awake, while during sleep, when the lids are comparatively motionless, the removal of edema fluid by the lymphatics would be less active.

In the 2 subjects in whom there was a superficial vein of the eyelid sufficiently large for direct determination of venous pressure, the venous pressure was found to be lower with the subjects in the sitting than in the supine position. These observations, though limited to only 2 subjects, suggest strongly that the hydrostatic, or filtration, pressure in the capillaries of the eyelids is decreased when a subject assumes an upright position. Landis¹⁷ has shown that elevation of the hand above the level of the heart decreases the hydrostatic, or capillary, blood pressure. There is no reason to doubt the occurrence of a similar effect in the capillaries of the eyelid when a person assumes an upright position and the eyelids are above the level of the heart. Therefore, interstitial fluid would tend to accumulate more rapidly with the subject in the supine than in the upright position because of the variations in venous pressure in the respective positions. On the basis of venous pressure alone, it might be expected that, in a person suffering from a condition tending to produce edema generally, edema would be more likely to develop in the lids at night during sleep and would disappear more readily during the day, when he is upright.

The eyelids are peculiar anatomically in that they enclose anteriorly a pyramidal space, the orbit, containing incompressible material surrounded, except at its anterior surface, or base, by rigid bony walls and relatively incompressible material. In order for any material to accumulate in the orbit, it would have either to displace blood from the adjacent vessels or to push tissue and fluids anteriorly, where the walls are distensible. It is unlikely that only blood would be displaced, and then, if at all, probably to only a minor extent, unless the localized tissue

17 Landis, E. M. Micro-Injection Studies of Capillary Blood Pressure in Human Skin, *Heart* 15 209, 1930.

pressure exceeded the arterial diastolic pressure, a condition which is unlikely in edema. Furthermore, with diffuse moderate compression of blood vessels, intravascular pressure in the compressed vessels, capillaries, venules and small veins would be built up from the arterial side to reestablish blood flow. It has been shown that in edema the tissue pressure is unlikely to increase sufficiently to exceed even capillary blood pressure for any great length of time^{18a}. It appears, therefore, on a purely theoretic basis, that edema fluid which accumulates in the posterior orbital space, tending to raise tissue pressure locally, will flow intercellularly into the distensible eyelids, where tissue pressure is and remains relatively low even in the presence of much edema. The studies of Charpy and Clermont¹⁸ tend to support this reasoning. They injected colored gelatin into the posterior orbital spaces of fresh cadavers and noted bulging of the tissues anteriorly, with an occasional rupture of the nasal portion of the orbital septum and escape of the material into the lids. In 1 instance the colored gelatin flowed freely from the posterior orbital space into the lids and filled the subcutaneous tissues. In the orbits injected by these observers, the material did not progress posteriorly, but invariably migrated anteriorly. With rapid injections the orbital septum acted as a barrier to the escape of the material into the eyelids. On the other hand, the authors stated that with a gradual accumulation of interstitial fluid, as in edema, the interstitial fluid would diffuse freely through the orbital septum and lodge in the subcutaneous tissues of the eyelids. Heerfordt¹⁹ obtained essentially the same results in cadavers after the injection of air into the posterior orbital space. The increase in volume noted for the tissues anterior to the orbits of 2 dogs after the injection of physiologic solution of sodium chloride into the posterior orbital spaces (see page 491) lends further support to the idea that interstitial fluid which tends to accumulate in the posterior orbital space probably migrates anteriorly into the subcutaneous tissues of the lids. In the four orbits injected the total change in volume anteriorly was not equal to the total volume of physiologic solution of sodium chloride injected into the posterior region of the orbit. This is probably due in part to displacement of blood and errors in the method employed. The lag in the change in volume anteriorly after the injection of fluid into the orbits is probably due to the reaccumulation of displaced blood and also to seepage of the injected solution into the anterior tissues of the orbit.

18 Charpy and Clermont. Structure topographique des paupières et épanchements intrapalpébraux, *Bibliog anat* **21** 65, 1911

19 Heerfordt, C. F. Ueber das Emphysem der Orbita, *Arch f Ophth* **58** 123, 1904

Although the venous pressure and lymph flow of the face are affected by postural changes in essentially the same way as are those of the eyelids the effects on tissue distensibility are different as shown by the studies of tissue pressure and skin distensibility. These structures differ further in that the eyelids probably accommodate most of the excessive amount of interstitial fluid that escapes into the intraorbital space as well as that which escapes into the tissue spaces of the eyelids themselves. The tissues of the face like those of other areas of the body studied accommodate only the fluid escaping into them. On the basis of these observations therefore edema would be expected to develop more readily in the eyelids than in adjacent areas namely the face.

It is more than likely that in a disease tending to produce edema generally, such as acute hemorrhagic nephritis edema fluid accumulating in the intraorbital space migrates into the distensible eyelids, thus making the eyelids swell more than they would if they had to accommodate only the edema fluid accumulating in the lids themselves. This might render the eyelids clinically edematous before other areas of the body in which a similar anatomic peculiarity does not exist. As Drury and Jones²⁰ have shown it is necessary for a part to increase approximately 8 per cent in volume before clinical edema is manifested and since the eyelids probably accommodate interstitial fluid accumulating in the whole orbit as well as in their own tissues the lids might experience an increase of 8 per cent in volume before other areas which accommodate only the fluid escaping into their own tissues.

SUMMARY

The mean subcutaneous tissue pressure in the lower eyelids of 21 normal subjects was found to be 23.4 ± 0.7 mm. of water with a standard deviation of 5.1 ± 0.5 mm. The minimum and maximum variations were 16 and 32 mm. of water, respectively. Subcutaneous tissue pressure in the eyelids remained practically the same when 1.0 cc. of a physiologic solution of sodium chloride was injected subcutaneously. There was a definite rise in the subcutaneous tissue pressure when a similar amount of physiologic solution of sodium chloride was injected subcutaneously into the loose pendulous breasts and loose abdominal wall of a multipara and into the prepuce and there was a comparatively marked rise when the solution was injected into the subcutaneous tissue of the volar surface of the forearm and the pretibial area. Even with marked edema of the eyelids due to various causes the subcutaneous tissue pressure of the lids increased relatively little.

²⁰ Drury, A. N. and Jones, N. W. Observations upon the Rate at Which Edema Forms When the Veins of the Human Limbs Are Congested. *Heart* 14: 55, 1927.

The skin of 20 lower eyelids was found to be very distensible, having a mean distensibility ("stretchability") of 1.23 ± 0.06 mm of stretch per centimeter of skin per 20 Gm of force, with minimum and maximum variations of 0.56 and 2.26 mm, respectively. The standard deviation was 0.43 ± 0.05 mm. The distensibility of the skin of the eyelids was found to be approximately five times that of the pretibial area, four times that of the dorsum of the foot, two and a half times that of the volar surface of the forearm, twice that of the face, one and three-fourths times that of the dorsum of the hand and one and two-tenths that of the abdomen.

The linear rate of lymph flow in the superficial lymphatics of the skin of the eyelids with the subject resting quietly in the supine position was found to be increased by blinking or by the subject's merely assuming the sitting position.

Direct determinations of the venous pressure in the veins of the lower lid of 2 subjects without venous obstruction and with veins sufficiently large for venipuncture showed a marked decrease when the subjects changed from the supine to the sitting position.

The injection of physiologic solution of sodium chloride into the posterior orbital area of dogs increased the volume of the anterior tissues of the orbit. This increase was considered an indication of a probable migration anteriorly of edematous fluid, which escapes to the only freely distensible portion of the rigidly enclosed orbit containing incompressible material.

CONCLUSIONS

These data indicate that in the eyelids of a subject suffering from a condition tending to produce edema equally throughout the body, such as acute hemorrhagic nephritis, edema would develop more readily and probably earlier than in other common sites of edema because of the marked distensibility of the eyelids, the absence of early and marked benefits from the local tissue pressure and restraining skin in limiting formation of edema and the fact that the lids accommodate not only the edema fluid escaping into their own tissues but also that of the whole orbital cavity. The edema would be most apt to develop early during sleep because at that time the lymph flow is most sluggish, movement of the lids and gravitational effects favoring lymph flow are at a minimum and venous pressure is most marked. Conversely, the edema would be expected to disappear during the day, when the patient is up and about.

PEPTIC ULCER AND ACHLORHYDRIA

A FURTHER STUDY OF THE ROLE OF ACID GASTRIC JUICE
IN THE PATHOGENESIS OF PEPTIC ULCER

WALTER LINCOLN PALMER, M D

AND

PAUL B NUTTER, M D

CHICAGO

The concept that acid gastric juice plays an essential role in the genesis of peptic ulcer is supported by a great deal of clinical, pathologic and experimental evidence. A number of points, however, are not yet clear. Apparently incompatible with this thesis is the alleged occurrence of chronic ulcer with achlorhydria. In this paper we wish to consider the question as to whether or not peptic ulcer occurs in the complete absence of acid gastric juice.

In 1926 one of us (W L P) reviewed the literature on this subject, studied a group of cases and concluded that there was no *conclusive* evidence that chronic ulcer occurs in the complete absence of acid gastric juice¹. The evidence usually offered to prove that ulcer may occur in the presence of achlorhydria was found inadequate either in demonstrating achlorhydria or in establishing the presence of chronic benign ulcer, or, indeed, in both respects. It was pointed out that before the diagnosis of ulcer with anacidity may be made the anacidity must be "histamine proved" and the ulcer must be shown not only to be present but to be not syphilitic, tuberculous or carcinomatous. In a series of over 1,000 cases of gastric and duodenal ulcer studied at that time, no instance of chronic benign ulcer occurring in the presence of complete achlorhydria was found.

Since then, various authors have reported instances of "ulcer with achlorhydria". Cheney,² in 1927, described a case of chronic benign gastric ulcer in which two evening samples of gastric juice failed to show any free acid and the continuous quantitative estimation of

From the Department of Medicine, the University of Chicago

A brief resumé of this paper was presented before the Association of American Physicians at Atlantic City, N J, May 2, 1939

1 Palmer, W L. The Mechanism of Pain in Gastric and Duodenal Ulcers I Achlorhydria, Arch Int. Med **38** 603 (Nov) 1926

2 Cheney, G. Peptic Ulcer and Achlorhydria, California & West Med **27** 78, 1927

gastric secretion by the method of Bloomfield and Keefer³ showed very low ten minute secretions, rapid emptying time and no acid reaction to Topfer's reagent or to neutral red in any of the specimens, the total acidity reaching only 6 degrees. At operation an "almost completely healed ulcer measuring 3 by 4 cm" was found. It is significant that no histamine test was carried out and that an Ewald test meal six months earlier had shown free acidity of 26 and total acidity of 39 degrees. Apparently the stomach was able to secrete acid gastric juice at the time the ulcer developed.

Wilson and Earl⁴ described a case of gastric ulcer in which repeated Ewald test meals failed to disclose free acid whereas a fractional histamine test revealed a maximum free acidity of 16. "At operation a small, indurated, partially healed ulcer with a shallow crater, 4 mm in diameter, and a zone of induration of 1.5 cm diameter was found.

The microscopic sections gave no evidence of malignancy." In a second case of gastric ulcer described by these authors the Ewald test meal yielded no free hydrochloric acid, but the histamine test disclosed the maximum of free acidity to be 32 degrees.

Abramson⁵ found the evidence demanded by Palmer "too severe" and estimated that the incidence of achlorhydria in cases of gastric ulcer was 13.5 per cent. In a series of 89 cases, he observed 3 in which no free acid was found by fractional analysis after a rusk test meal (a modified Ewald) or after histamine given simultaneously with a rusk test meal. Two of these 3 cases were so-called recent cases. Further details were not given. These cases may indeed have been instances of chronic ulcer with complete and persistent achlorhydria, but the report is too brief to be completely convincing. Miller, Prendergrass and Andrews,⁶ in a study of 30 cases of gastric ulcer, found 1 instance of achlorhydria, but here also the evidence for the diagnosis was based on a single Ewald test meal and was therefore insufficient. The case of active duodenal ulcer described by Brambridge⁷ was adequately proved so far as the presence of active ulcer was concerned,

3 Bloomfield, A. L., and Keefer, C. S. A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man, *Arch. Int. Med.* **37**: 819 (June) 1926.

4 Wilson, J. A., and Earl, G. Achlorhydria and Hypochlorhydria in Peptic Ulcer, *Minnesota Med.* **15**: 79, 1932.

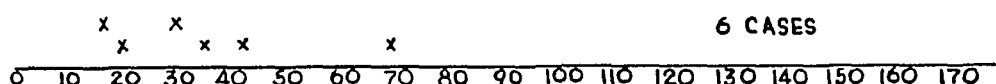
5 Abramson, L. Occurrence of Achlorhydria in Gastric and Duodenal Ulcer, *Acta med. Scandinav.* **77**: 77, 1931.

6 Miller, T. G., Prendergrass, E. P., and Andrews, K. S. A Statistical Study of Clinical and Laboratory Findings in Gastric and Duodenal Ulcer, *Am. J. M. Sc.* **177**: 15, 1929.

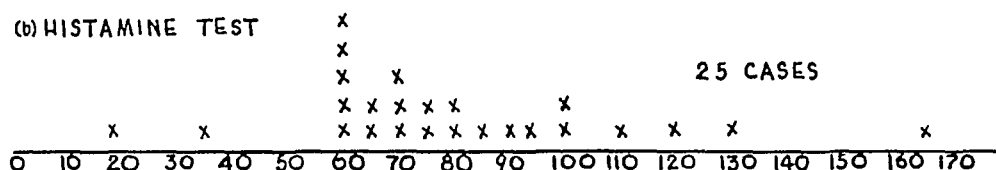
7 Brambridge, C. V. An Unusual Case of Duodenal Ulcer, *East African M. J.* **14**: 172, 1937.

but the diagnosis of achlorhydria rested on a single fractional test meal (type not stated) Moutier and Colmenares⁸ stated that one of them had encountered 2 cases of gastric ulcer with achlorhydria, but they gave no details Vanzant, Berkson, Alvarez and Eusterman,⁹ after reviewing the literature, concluded that achlorhydria "is present just as often in patients with ulcer of the stomach as in normal persons" If this is true, the incidence of anacidity, as demonstrated by the histamine test, in patients with chronic gastric ulcer should be over 10 per cent, for Bloomfield and Pollard¹⁰ found the incidence in normal persons to be 11.9 per cent We have not been able to find satisfactory evidence of such an incidence in patients with chronic gastric ulcer

(a) FASTING SECRETION, ALCOHOL TEST MEAL OR "CONTROL" ANALYSIS



(b) HISTAMINE TEST



(c) EWALD TEST MEAL

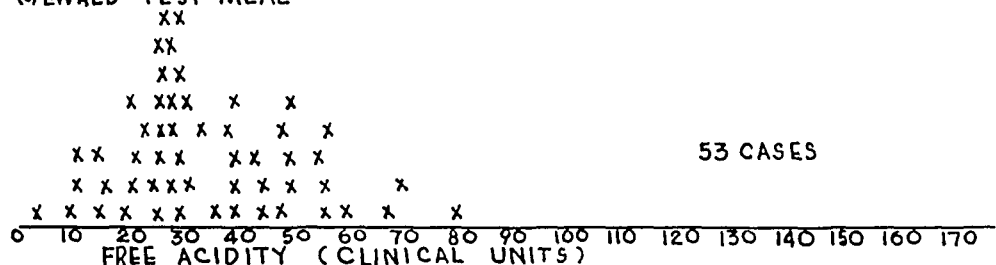


Fig 1—Maximum free acidity of gastric contents recorded after various tests in 84 cases of gastric ulcer

Gutzeit¹¹ described an acute ulcer seen gastroscopically in the stomach of a patient with pernicious anemia and histamine-proved

8 Moutier, F, and Colmenares, J. Ulcère duodenal avec achlorhydrie chez un syphilitique, *Arch d mal de l'app digestif* **27** 980, 1937

9 Vanzant, F R, Berkson, J, Alvarez, W C, and Eusterman, G B. Changes in Gastric Acidity Associated with Peptic Ulcer, Cholecystitis, and Other Diseases, Analyzed with the Help of a New and Accurate Technique, *Arch Int Med* **52** 616 (Oct) 1933

10 Bloomfield, A L, and Pollard, W S. Gastric Anacidity, New York, The Macmillan Company, 1933, p 53

11 Gutzeit, K. Die Gastroskopie im Rahmen der klinischen Magendiagnostik, Berlin, Julius Springer, 1929

achlorhydria Symptoms of ulcer were not present The accidental observation was not confirmed by further gastroscopic or roentgen examinations

Our own observations on acidity in cases of gastric ulcer in the past eleven years are summarized in the scatter diagram of figure 1 In 84 cases of chronic gastric ulcer no instance of complete and persistent achlorhydria was found In 1 instance the single gastric analysis made was carried out after an Ewald test meal and showed free acidity

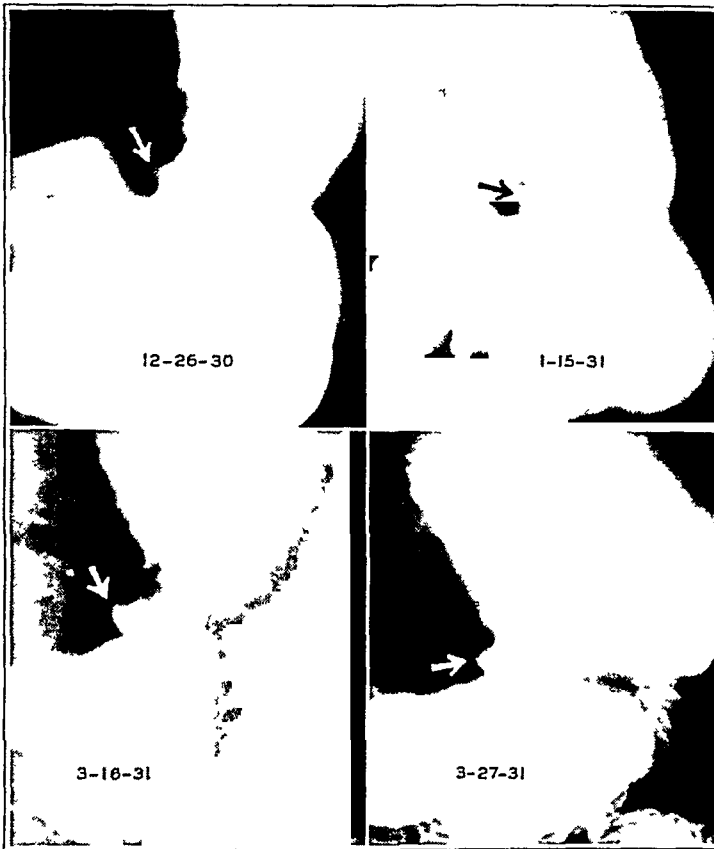


Fig 2 (case 1) —Small chronic gastric ulcer, with moderate hourglass deformity, associated with low gastric acidity (maximum free acidity after histamine, 18 degrees)

of only 4 A histamine test was not done It would almost surely have shown higher values

Three cases of our series are of such interest as to warrant rather detailed descriptions

REPORT OF CASES

CASE 1—A woman 51 years of age was admitted to the hospital Dec 11, 1930, because of abdominal distress, which conformed to the ulcer pattern, of two years' duration The pain had first appeared six years prior to her admission and had lasted until the patient was operated on two years after the onset The surgeon at that time found "an old healed peptic ulcer with marked cicatricial contraction"

and hourglass formation between the middle and lower thirds of the stomach, the scar was excised. Ewald test meals at that time were reported to have disclosed free acidity of only 10 and 12 degrees. The patient remained well for two years and then the distress recurred. At the time of admission to the hospital in 1930, roentgen examination disclosed a penetrating ulcer of the lesser curvature, with moderate hourglass formation (fig 2). The patient was poorly nourished, but there was neither clinical nor roentgen evidence of pulmonary tuberculosis. The blood Wassermann and Kahn tests were negative. Rather severe essential hypertension was present, the blood pressure ranging from 205 to 225 systolic and from 105 to 125 diastolic. Several gastric analyses gave the results summarized in table 1.

The patient obtained complete symptomatic relief with the usual treatment for ulcer. The crater decreased in size, as seen in roentgenograms, but did not disappear. Three months later, at operation the hourglass contracture was found, together with a hard ulcer about 0.7 cm in diameter. The ulcer was excised, examined microscopically and found to be benign. There has been no recurrence of the epigastric distress in the eight years since the operation. The patient has remained well except for the essential hypertension and its complications.

TABLE 1—*Course of Events in Case 1*

Date	Test Meal	Maximum Free Acidity
Dec 6, 1930	Motor meal (2 hours)	18
Dec 12	Ewald (45 minutes)	0
Dec 15	Alcohol (fractional)	0
Dec 17	Histamine (fractional)	0
Dec 22	Normal meal (3 hours)	10
Dec 31	Histamine (fractional)	12
March 25, 1931	Histamine (fractional)	18

It is of interest to note that one Ewald test meal, one fractional analysis after alcohol and one histamine test each failed to disclose free acidity, although a small amount of free acid had been found previously with a so-called motor meal and was shown to be present by a subsequent histamine test. The level of gastric secretion was obviously low—the lowest in the group studied. It is entirely possible that the gastric secretory response may have been greater at times than the test meals disclosed. The evidence suggests, however, that, while this was not an instance of chronic ulcer with complete achlorhydria, it was a case of chronic ulcer with very low acidity, similar to the case described by Wilson and Earl. The rather indolent, chronic nature of the lesion, with the definite hourglass formation, suggests a process of only moderate activity.

CASE 2—The course of events in this case is somewhat similar, and in some respects more striking.

A man was first admitted to the clinic in October 1932, at the age of 51. He gave a history of periodic epigastric distress of ten years' duration. The free acidity following an Ewald test meal was 50 degrees. The roentgenograms disclosed a large penetrating ulcer of the lesser curvature of the stomach, with a deep incisura on the greater curvature which almost amounted to an hourglass contracture. Complete symptomatic relief was obtained with medical treatment. The patient soon discontinued the use of alkali, however, and took it only occasionally.

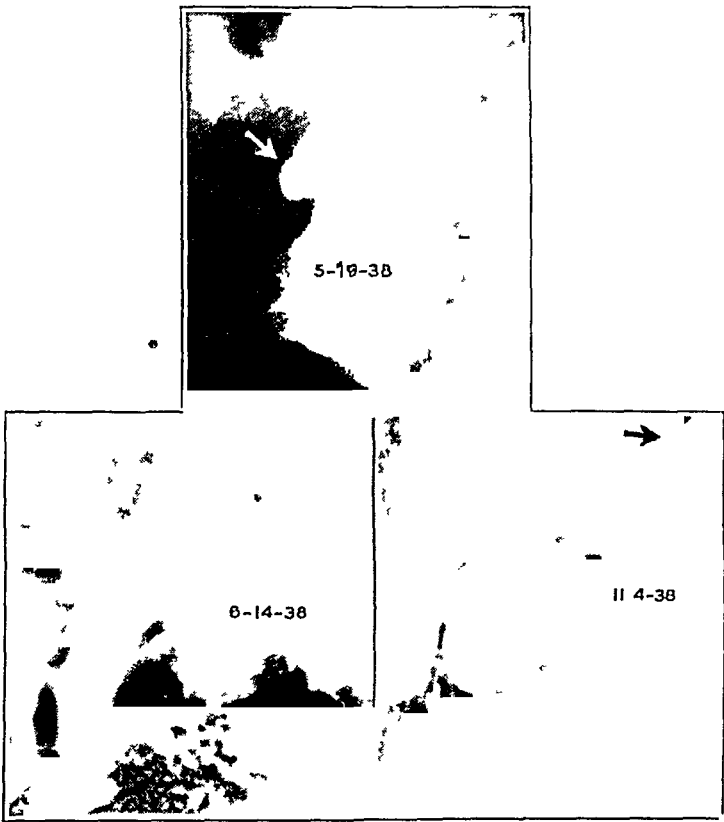


Fig 3 (case 2) —Chronic gastric ulcer, with hourglass deformity, associated with variable gastric secretory response (transitory achlorhydria demonstrated by histamine tests)

TABLE 2 —*Course of Events in Case 2*

Date	Maximum Degrees of Free Acidity	Gastroscopic Observations	Roentgenographic Observations
1932			
Oct 5	Ewald 50		Large ulcer with hour glass contracture
1938			
May 19			Large ulcer
May 25		Ulcer with tremendous inflammatory infiltration	
May 28	Histamine 0.6 mg 62		
June 1	Histamine 0.6 mg 33		
June 4	Histamine 0.6 mg 28		
June 8	Histamine 1.0 mg 5		
June 15	Histamine 1.0 mg 0	Two small superficial ulcers with slight inflammation	Very small ulcer with hourglass deformity
June 16	Histamine 1.0 mg 10		
June 27	Histamine 0.6 mg 45		
July 27		Ulcer freshly epithelized	
Aug 15	Histamine 0.6 mg 44		
Oct 8	Histamine 0.6 mg 64		
Oct 15	Histamine 0.6 mg 0		
Oct 19		Small ulcer with marked gastritis	
Oct 29	Histamine 0.6 mg 76		
Nov 4			Small ulcer with deformity
Nov 9	Histamine 0.6 mg 79		
Nov 12	Histamine 0.6 mg 79	Ulcer ?	Small ulcer with deformity
Nov 18			
Nov 19	Histamine 0.6 mg 0		

whenever slight distress recurred. In 1938, six years later, he returned with another rather severe attack of pain. Roentgenograms again revealed a penetrating gastric ulcer of the lesser curvature, with deformity of the greater curvature also. The Wassermann and Kahn tests of the blood were negative. The patient was thin and poorly nourished, but there was no evidence of extragastric disease. In the course of a few weeks of treatment, the ulcer crater, as seen in the roentgenograms, disappeared (fig 3). Gastroscoopically the ulcer was seen to heal, and the rather intense gastritis improved markedly. Later the ulcer recurred. The course of events is summarized in table 2. As the ulcer healed, the gastric secretory response to histamine decreased from 62 on May 28 to zero on June 15 and then gradually rose to a peak of 79 on November 9. The achlorhydria of October 15 and that of November 19 are difficult to explain. Perhaps they were due to errors in technic. In any event it is apparent that in this case of gastric ulcer there occurred a phase in which gastric secretion was diminished to the point of achlorhydria. During this phase, with continuance of the antacid therapy, the healing of the ulcer progressed and the inflammatory process in the gastric mucosa markedly improved. The hourglass deformity of the stomach in this instance suggests, as in the previous case, a rather indolent or only moderately active process.

The variation in the secretory response to histamine is indeed amazing. Schiff¹² observed the same phenomenon in an apparently normal stomach in which frequent histamine tests were carried out over a prolonged period. The cause was not apparent. The gastric mucosa, as seen through the gastroscope, was not significantly altered during the phase of achlorhydria. Seymour, Spies and Payne¹³ also noted that in certain cases the initial histamine test disclosed anacidity but subsequent tests disclosed the presence of free acid.

CASE 3—A woman aged 62 was admitted to the hospital Dec 7, 1936, complaining that she had experienced continued epigastric pain and vomiting for sixteen days. Periodic gnawing epigastric distress had been present for ten months prior to admission. The fractional gastric analysis after histamine stimulation disclosed a maximum of free acidity of 75 degrees. An enormous penetrating ulcer of the lesser curvature of the stomach was found, and its course to complete healing in April 1937 was followed by means of roentgenograms (fig 4) and the gastroscope. The course of events is outlined in table 3.

No recurrence of a lesion was found until Oct 22, 1938, when Dr Rudolf Schindler observed through the gastroscope a "very definite crater-like, though not very deep, ulcer on the lesser curvature. Its floor was yellowish, its edges were sharp, and it was surrounded by a red halo." It was not seen in the roentgenograms taken on November 1, but on November 16 Dr Schindler again saw the ulcer, which looked just as it had at the examination one month previously. On December 9 he found that it had healed completely. The patient did not complain of distress during the time the ulcer was present but, on questioning, admitted that she had at times noticed "a little gnawing feeling," relieved by an alkaline powder or by milk.

The lesion recurred in March 1939. The patient did not experience so-called "ulcer pain," although she admitted that on March 4 there was generalized

12 Schiff, L. Gastric Secretion in Man. Observations on the Effects of Repeated Injections of Histamine and on Transient Achlorhydria, *Arch Int Med* 61: 774 (May) 1938.

13 Seymour, W. B., Spies, T. D., and Payne, W. The Gastric Secretion in Chronic Alcoholic Addiction, *J Clin Investigation* 13: 15, 1939.

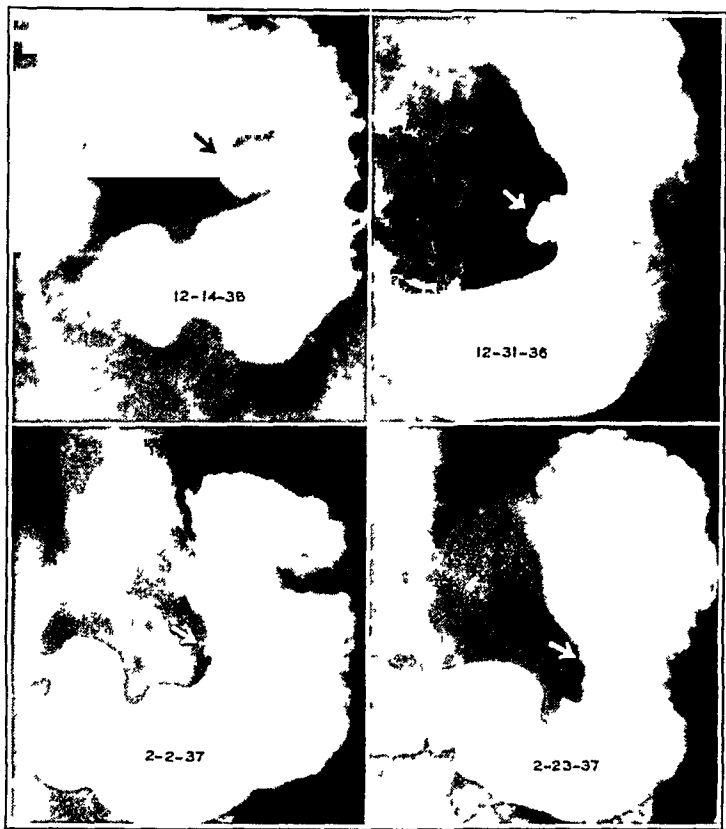


Fig 4 (case 3) —Chronic gastric ulcer with rapid healing (free acidity at histamine test, 75 degrees)

TABLE 3—*Course of Events in Case 3*

Date	Maximum Degrees of Free Acidity After 0.5 Mg Histamine	Gastroscopic Observations	Roentgenographic Observations
December 1936	75	Large ulcer	Enormous ulcer
April 1937 to September 1938 (repeated examinations)	10 to 23	Always healed	Always healed
Oct 18, 1938	20	Shallow ulcer	
Oct 22			
Oct 28	10		
Nov 1			Healed
Nov 11	22		
Nov 16		Healing	
Dec 9		Healed	
Jan 9, 1939	17	Healed	
Feb 28	4		
March 3		Shallow ulcer	
March 4	0		Very small ulcer (2 mm in diameter)
March 6			
March 8		Shallow ulcer	
March 10	0		
March 13			Healed
March 15		Almost healed	
March 20	20		
March 27		Healed	
April 5	0	Healed	
April 19	18	Very shallow ulcer	Very small ulcer (2 mm in diameter)
April 21	32*		Healed
April 24		Healed	

* Alcohol test meal

abdominal soreness or discomfort, which was not severe and was somewhat intensified by eating. On the other hand, on March 10 and again on March 15 she stated that there had been no pain—"Nothing bothers me"—and on March 27, when the ulcers were found gastroscopically to be healed, she again admitted the presence of mild epigastric "soreness—just soreness." It was felt that no reliance could be placed on the statements of the patient. She made no complaints at the time of the shallow ulceration found in April 1939. The conclusion was reached that if symptoms were present they were indeed mild.

The free acidity, 75 degrees, present in 1936 at the time the large ulcer was observed is certainly acceptable as acidity. The drop in the gastric secretion and the weak response to histamine after April 1937 are difficult to understand. Per-

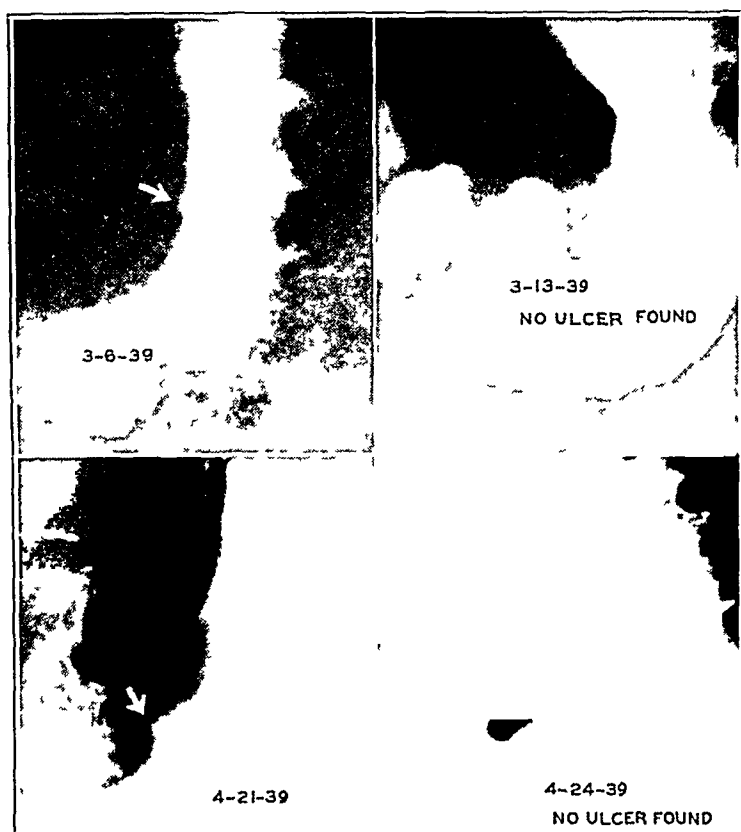


Fig 5 (case 3) —Acute transitory gastric ulcers, hardly discernible roentgenologically, associated with low gastric acidity and transient achlorhydria

haps they might be attributed to the atrophic gastritis which Dr Schindler observed in variable degrees from time to time. The small, shallow ulcer observed gastroscopically on Oct 22, 1938, during the period of low secretory response, was not found in the roentgenographic examination on November 1. On November 11 gastroscopic examination showed the lesion to be healing, and on December 9 it was healed. Apparently it was a superficial acute or subacute ulcer. A small shallow ulcer was found again by gastroscopic examination on March 3, 1939, and by roentgenologic examination on March 6. It was still seen through the gastroscope on March 8, but the roentgenograms failed to disclose it on March 13. On March 20 it was almost healed, and on April 5 it was healed. A shallow lesion was again visible through the gastroscope on April 19 and could be detected on the roentgenogram two days later. On April 21, however, it could not be

demonstrated by either gastroscopic or roentgenologic examination. No free acid was found after the injection of histamine on March 4, March 10 or April 5, and a maximum of 20 units was found on March 20. This is the most persistently low secretion of acid that we have observed in a patient with ulcer. The lesion demonstrated during the period of achlorhydria and the two occurring in the presence of very low acidity were small, superficial and barely detectable in the roentgenograms (fig 5), and they healed promptly, hence they seemed obviously to have been acute or subacute rather than chronic ulcers.

COMMENT

Rodgers and Jones¹⁴ recently described a type of acute or subacute small gastric ulcer, 2 to 5 mm in diameter, which is not found roentgenologically but is found gastroscoically only in the presence of a "thin atrophic mucosa and associated with absence or diminution in the secretion of acid." In 7 of their 17 cases achlorhydria was shown after the injection of histamine (presumably, a single test). One of the patients had pernicious anemia and a strongly positive Wassermann reaction. In 3 patients given gastroscopic examination after intervals of two to four weeks, the ulcers were found to have disappeared. The authors stated that they had never seen "large chronic gastric ulcers in patients with a uniformly thin gastric mucosa and either a low acid curve or achlorhydria."

The statement just cited and, indeed, the other observations of Rodgers and Jones are quite in accord with our own experience. Apparently acute and subacute ulcers may develop in the stomach in the presence of achlorhydria, but such lesions do not become chronic nor are they of large size. Acid gastric juice is essential for the development of large chronic ulcers, the typical ulcers of Cruveilhier. Important confirmation of this view is given by the failure of Kahn¹⁵ to find a single chronic, or indeed, acute, peptic ulcer at autopsy in 840 cases of pernicious anemia, and by the apparent failure of Washburn and Rozendaal¹⁶ to find such an ulcer in 906 consecutive cases of pernicious anemia. Murphy and Howard¹⁷ referred to 4 instances of duodenal ulcer encountered in 440 cases of pernicious anemia, but no evidence, clinical or roentgenologic, was presented to show that the alleged ulcer was active.

14 Rodgers, H. W., and Jones, F. A. Subacute Ulceration of the Stomach Associated with Atrophy of the Gastric Mucosa and with Absence or Diminution in the Secretion of Hydrochloric Acid, *St. Barth. Hosp. Rep.* **71** 140, 1938.

15 Kahn, J. R. Absence of Peptic Ulcer in Pernicious Anemia, *Am. J. M. Sc.* **194** 463, 1937.

16 Washburn, R. N., and Rozendaal, H. M. Gastric Lesions Associated with Pernicious Anemia, *Ann. Int. Med.* **11** 2172, 1937.

17 Murphy, W. P., and Howard, I. An Analysis of the Complications Occurring in a Series of Patients with Pernicious Anemia, *Rev. Gastroenterol.* **3** 98, 1936.

CONCLUSIONS

1 Small acute and subacute gastric ulcers may occur in the presence of achlorhydria proved by the histamine test

2 Large chronic gastric ulcers occur only in the presence of acid gastric juice

3 Acid gastric juice plays an essential role in the genesis and course of chronic gastric ulcer

ADDENDUM

Since the completion of the work just described, a paper by Ruffin and Dick¹⁸ has appeared in which an incidence of achlorhydria in cases of active duodenal ulcer of 5.4 per cent (24 of 419 cases) was reported, as well as a similar incidence in cases of gastric ulcer, 6.7 per cent (3 of 42 cases). Apparently the diagnosis of achlorhydria was based on a single determination (histamine). The fallacy inherent in such an analysis has already been pointed out, but it may be illustrated further by the following brief report.

A man 48 years of age entered the hospital June 7, 1939, with a history of epigastric distress of ten years' duration. The stools had been tarry one month prior to admission. Gastric ulcer was found gastroscopically and roentgenologically. The following gastric analyses were carried out:

Date	Stimulus	Free Acidity (Maximum)
June 15	Histamine, 0.5 mg	0
18	Histamine, 0.5 mg	0
24	Histamine, 0.5 mg	0 (Tip of the tube shown fluoroscopically to be in stomach)
25	Histamine, 0.5 mg	0 (p_H 3.49)
30	Histamine, 0.5 mg	52 (p_H 1.50)
30	Histamine, 1 mg	76 (p_H 1.50)
30	Histamine, 1 mg and 100 cc of 7% alcohol	68 (p_H 1.61)

Subtotal gastrectomy was performed by Dr. Phemister July 5. Two small healing gastric ulcers were found in the resected specimen.

In the University Clinics gastric analysis has been carried out for patients with digestive complaints routinely and on the whole with few exceptions during the past twelve years. In a series of over 2,200 cases of proved (roentgenologically, gastroscopically or by operation) active gastric or duodenal ulcer, no instance of complete and persistent achlorhydria has been encountered.

¹⁸ Ruffin, J. M., and Dick, M. The Significance of Gastric Acidity After Histamine Stimulation. A Statistical Study of 2877 Gastric Analyses, *Ann. Int. Med.* **12** 1940, 1939.

HYDATID CYSTS OF THE LUNG

CAMERON HAIGHT, M D

AND

JOHN ALEXANDER, M D

ANN ARBOR, MICH

The infrequent occurrence of hydatids of the lung in North America prompts the recording of 2 cases and a review of the recent literature. Although echinococcus disease is prevalent in Australia, Iceland, South America and some of the Mediterranean countries, only 44 cases of pulmonary and pleural echinococcus cysts are to be found in the literature of the United States and Canada. Thirty-four of these cases were collected in 1930 by Phillips,¹ who added 2 cases of his own. The 8 cases subsequently reported or referred to and the 2 cases reported in this article make a total of 46 known cases.

The nativity of a few of the patients whose cases have been reported is not known, yet it is of interest that hydatid disease of the lung has occurred in only 5 patients known to have been born in North America (Garrett,² Magath,³ Phillips' case,¹ Johns⁴ and Leslie⁵). Both the patients who are the subject of this report had emigrated from countries in which the disease is prevalent, and the probability is great that the infestation occurred prior to their entrance into this country. Since the disease may occasionally be encountered in this country, it should be considered in the differential diagnosis of pulmonary lesions resembling hydatid disease. The difficulties in diagnosis are well illustrated in case 2, in which the correct diagnosis was not made until three years after the patient reported for treatment. A discussion of the symptoms, diagnosis and treatment of pulmonary hydatids will be omitted in this article, as these aspects have been fully presented in the

From the Department of Surgery, University of Michigan

1 Phillips, E W. Hydatid Cysts of the Lung. Review of the Recorded North American Cases, *Arch Surg* **21** 1324-1377 (Dec) 1930

2 Garrett, R E. Hydatid Cysts, with a Report of a Case, *Maryland M J* **49** 373-378, 1906

3 Magath, T B. Echinococcus Disease. Etiology and Laboratory Aids to Diagnosis, *M Clin North America* **5** 549-571 (Sept) 1921

4 Johns, F S, in discussion on Phillips¹

5 Leslie, C J. Pulmonary Echinococcosis, *Am J Dis Child* **55** 1267-1272 (June) 1938

excellent and comprehensive writings of Phillips,¹ Dew,⁶ Dévé,⁷ Carayannopoulos⁸ and Godfrey⁹

REPORT OF CASES

CASE 1—*Hydatids of pleura drained by thoracotomy in another hospital in 1923, reappearance in lung in 1931, operative removal, with apparent cure*

History—P. P., a man aged 30, was admitted to the University Hospital on Sept 16, 1931, complaining of cough, sputum and sweating. The patient was born in Greece, and during his childhood he often played with dogs when visiting his father's sheep ranch. At the age of 14 he emigrated to this country. He was in good health until a year or two later, when he suffered from a cough which was diagnosed as whooping cough. A month after the onset of the cough a sharp pleuritic pain developed in the lower right portion of the chest anterolaterally. He returned to Greece for seven months, and on his arrival there the cough disappeared. Because of continuation of the pain, he was examined by several physicians, whose findings were negative. Roentgenograms of the chest were not taken. On his return to this country, the pain disappeared and he felt well until 1923, when there developed a "cold" and a severe pain of sudden onset in the right side. A diagnosis of pleural effusion was made, and a thoracotomy was performed on the right side. The nature of the observations at operation is not known, as no report could be obtained from the surgeon or hospital. During the daily dressings the patient noticed that numerous whitish gray cysts, 1.5 to 2 cm in diameter, were expelled from the wound. They were examined, and the patient was told they were echinococcus cysts. The thoracotomy wound became too small for adequate drainage, and a second operation was performed. After this the wound healed, and a roentgenologic examination revealed no further disease. The patient then felt well and had no symptoms except when he had a "cold," at which time there would be a small amount of blood-streaked sputum and occasional mild pain in the region of the thoracotomy scar.

In September 1931, the pain recurred in the right lower portion of the thorax anterolaterally and was accompanied by perspiration, cough and expectoration of dark gray, foul sputum, which had a "burning taste." Eight days later the patient expectorated a "broken cyst," similar in appearance to the cysts which had been discharged through the thoracotomy opening eight years previously. During the next eight days prior to his admission, he expectorated some blood, several cysts and about a cupful of sputum daily.

Physical Examination—There were marked pallor, profuse diaphoresis, moderate cough and expectoration and less than 1 degree (F) of fever. Excursion of the right part of the thorax was decreased, and a depressed scar, 5 cm in length, was visible on this side in the region of the sixth and seventh ribs between the anterior and the posterior axillary line. Extending upward and

6 Dew, H. R. Hydatid Disease. Its Pathology, Diagnosis and Treatment, Sydney, Australasian Medical Publishing Company, Ltd., 1928, Some Aspects of Echinococcus Disease, Surgery **2** 363-380 (Sept.) 1937.

7 Dévé, F. Trente-deux années d'étude de l'échinococcose, Prensa méd argnt **19** 523-534 (Aug.) 1932.

8 Carayannopoulos, G. Contribution to the Diagnosis and Treatment of Hydatid Cysts of the Lung, Ann Surg **100** 125-147 (July) 1934.

9 Godfrey, M. F. Hydatid Disease. Clinical, Laboratory and Roentgenographic Observations, Arch Int Med **60** 783-804 (Nov.) 1937.

backward from the scar was an area, measuring about 10 by 8 cm, over which there were dullness, absence of breath sounds and decrease in tactile fremitus. The other findings in the physical examination were not significant.

The hemoglobin content was 73 per cent, the white blood cells numbered 11,900 and the blood smear showed eosinophilia (8 per cent). Roentgenograms (fig 1) disclosed a large, relatively smooth-walled, rounded mass occupying the lower outer quadrant of the right part of the thorax. In the lateral view the mass was seen to be slightly posterior. The right portion of the diaphragm appeared to be drawn upward toward the mass, suggesting the possibility of a communicating track between the liver and the pulmonary mass. On roentgenoscopic examination there appeared to be a definite connection between the mass and the diaphragm (Dr F J Hodges). Examination of the cysts which had been expectorated revealed a laminated wall and many hooklets typical of *Taenia echinococcus*.

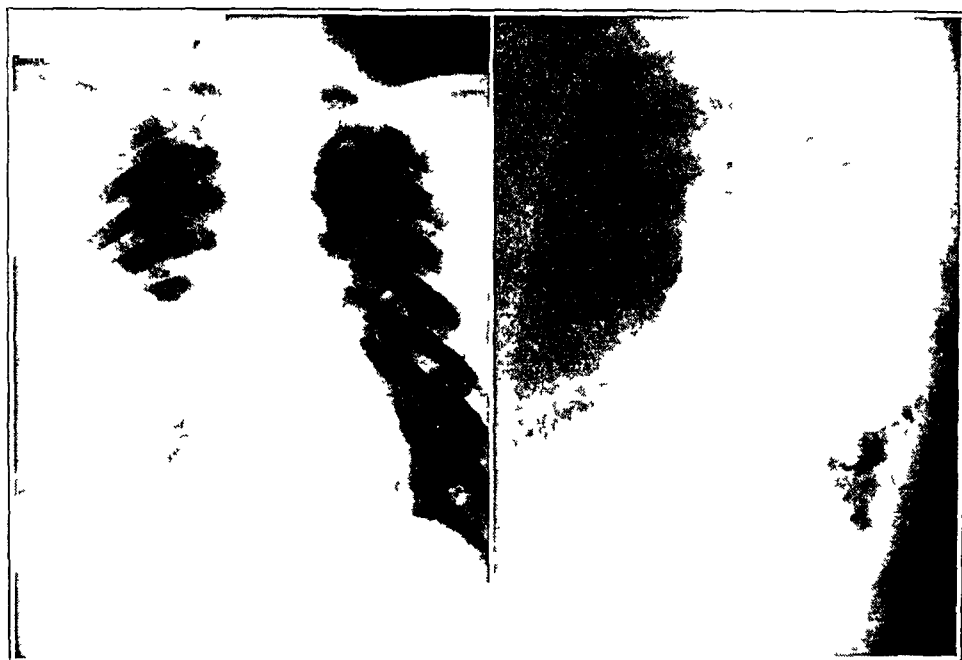


Fig 1 (case 1) —Frontal and lateral roentgenograms (Sept 16, 1931) showing area of density in the lower right portion of the chest. Communication with the liver is suggested by the roentgenograms, but was not demonstrated at operation.

Operation—First Stage of Removal of Pulmonary Echinococcus Cyst (Sept 17, 1931). An incision was made in the sixth intercostal space and through the parietal pleura anteriorly. The lung was adherent to the thoracic wall only around the site of the previous incision for drainage and slightly superior and posterior to it. In order to cause pleural adhesions to form before the cyst was removed, portions of the fifth and sixth ribs and the intervening intercostal muscle were resected. The exposed parietal pleura was covered with gauze, and the wound was closed without drainage. Pleural effusion developed, and thoracenteses were performed on the fourth, sixth, eighth and fourteenth postoperative days, with the removal of a total amount of 500 cc of serosanguineous fluid. The second stage of the drainage operation was delayed because of the development of thrombophlebitis of the left leg.

Second Stage, Evacuation of Mother and Daughter Cysts from Base of Right Lung (October 14) The incision was reopened and the gauze pack removed. For complete exposure of the cyst a long segment of the seventh rib was resected. The moment the periosteum was stripped from the posterior surface of this rib, the white wall of the cyst presented and ruptured. The opening into the cyst was enlarged, and approximately fifteen cysts, some filled with fluid and some collapsed, were evacuated. The smallest was approximately 1 cm in diameter, and the largest, 9 cm in diameter, was believed to be the mother cyst (fig 2). The cavity from which these cysts were evacuated contained at least one open bronchus and many small chambers which presumably housed cysts. One of these



Fig 2 (case 1) —Mother and daughter cysts removed from pulmonary parenchyma

chambers communicated with the main chamber only by a narrow track, and on dilatation of its mouth a cyst was evacuated. Inspection of the diaphragmatic aspect of the large defect within the lower lobe of the right lung showed no evidence of communication with the subphrenic space or the liver. In order to obtain complete exposure of the space within the lung, the hitherto unopened portions of the cortex of the lung, which covered the space peripherally, were incised radially between mattress sutures. The space within the lung was wiped with dilute solution of formaldehyde U S P (1:50), as was the extrapleural wound which had been contaminated by the cyst wall. Gauze packs, which had

been treated with petrolatum, were placed in the pulmonary defect, which after the evacuation of the cysts measured approximately 10 cm in diameter. The anterior and posterior angles of the incision were loosely closed. At the conclusion of the operation it was believed that there was no portion of any cyst wall remaining.

Pathologic examination of the mother cyst showed the wall of an echinococcus cyst with purulent infiltration. The numerous daughter cysts were in various stages of formation. A biopsy specimen of the incised pulmonary tissue lateral to the cyst revealed chronic purulent inflammation and fibroid pneumonia. A biopsy specimen from the thoracic wall did not show animal membrane.

Course—The postoperative convalescence was uneventful. In order to facilitate the closure of the large pulmonary defect, a temporary interruption of the right phrenic nerve was effected on October 23. The wound closed rapidly, and on

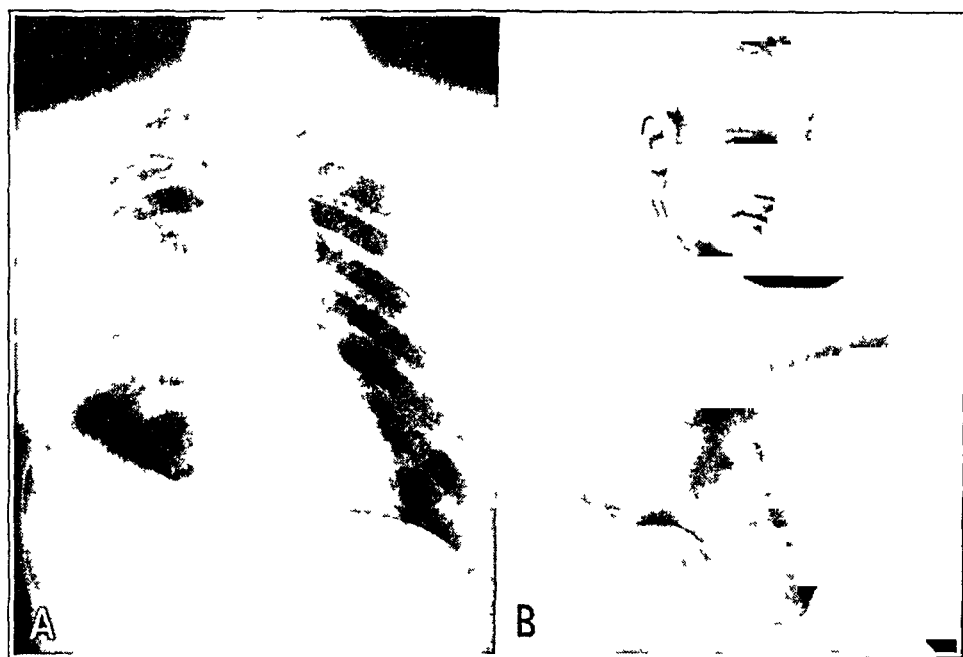


Fig 3 (case 1)—*A*, roentgenogram taken seven years after operation, showing no evidence of recurrence of cysts. Residual pleural and parenchymal fibrosis is evident. *B*, photograph of patient, showing healed incision.

October 28 the patient was discharged from the hospital, at which time a bronchial fistula was still present. The fistula closed spontaneously after six weeks, and the wound was completely healed one month later. During this period the patient had a small amount (4 cc) of sputum, which had a "peculiar taste." This symptom disappeared five months after operation. The patient has been examined at intervals during the seven years that have elapsed since operation and has remained without symptoms. The wound is solidly healed. Roentgenoscopic examination shows limitation of function of the lateral portion of the right side of the diaphragm, presumably from adhesions, and roentgenograms show no evidence of recurrence. The patient was last seen on Oct 24, 1938, at which time a roentgenogram (fig 3) showed no change when compared with films made in 1934 and 1936.

CASE 2—Hydatid cyst of upper lobe of the left lung, spontaneous rupture into bronchus, with secondary infection of cyst, surgical exploration in 1928, with negative results, removal of cyst in 1931, apparent cure

History—C F, a man aged 25, a Dane, was admitted to the University Hospital in September 1928. In 1921, at the age of 18, he had gone to Argentina, where he remained for twenty months. During this time he worked on a large ranch where there were numerous sheep and dogs. He then came to the United States and had resided here since, being employed as a machinist and chauffeur.

The present illness began in October 1927 with a sharp pleuritic pain in the left side of the chest, located anteriorly near the nipple and posteriorly at the same level. The pain was worse on deep breathing, and there was a severe cough with the expectoration of a small amount of grayish, thick sputum. The symptoms continued until April 1928, when he had a severe coughing spell, during which "it felt like there was something in the chest that wanted to come up." He continued to cough, and suddenly there was a sensation of something being torn loose in the left side of the chest beneath the nipple, followed by a gush of a large amount of "pus," which came from the mouth and nose "as if out of a faucet." The sputum was foul, yellowish, thin and watery. The patient was admitted to a hospital, where, he said, his temperature was 105 F for several days. His condition gradually improved during a month's hospitalization, but the pain, cough and expectoration of foul sputum continued. In July 1928 hemoptyses began, and pneumothorax therapy was instituted. The pneumothorax aggravated the hemoptyses and was promptly discontinued. Operation was advised.

Physical Examination—The patient was well nourished. There were flatness on deep percussion, diminution of the voice and breath sounds and decreased excursion of the upper left portion of the chest in an area between the third and the sixth rib anteriorly. No rales were present, the heart was not displaced. The temperature was 99 to 100 F, the pulse rate 90 to 100, the respiratory rate 20 and the white cell count 13,200. Roentgenologic examination revealed what appeared to be a large collection of fluid in the upper left part of the chest. A preoperative diagnosis of interlobar empyema with bronchial fistula was made.

First Operation (Sept 20, 1928)—With the use of local anesthesia, exploratory thoracotomy was performed through an anterior axillary approach, with the removal of 10 cm of the fifth rib. Air from the recent pneumothorax was present in the pleural cavity. The upper lobe was adherent to the anterior thoracic wall. The lower lobe was adherent inferiorly and posteriorly, where it seemed infiltrated on palpation, and over this area of apparent infiltration aspiration was performed through the intact skin. No pus was found. The interlobar fissure was opened to the hilus of the lung without the finding of any fluid or abscess. Although no induration of the upper lobe was palpable through the thoracotomy incision, aspiration was likewise carried out through the intact skin in the region of the upper lobe where it was adherent to the thoracic wall, and no pus was found. It was then concluded that a pulmonary abscess rather than interlobar empyema was present and that the abscess was so small that it could not be palpated. The wound was closed, and the air from the pneumothorax was evacuated.

Course—The postoperative course was uneventful, and roentgenologic examination showed that the rounded mass seen previously had lost its definite contour. The patient was discharged on October 2. He had gained in weight and felt considerably improved.

In the interval between 1928 and his readmission in 1931, the patient worked regularly, and during most of the time he felt fairly well. He continued how-

ever, to expectorate a small amount of sputum, about 4 Gm daily, which had an offensive taste and was occasionally blood streaked. In February 1929, a diagnostic bronchoscopic examination showed inflammation of the left bronchial tree. During the several months preceding his readmission to the hospital on Oct 13, 1931, there had been an increase in the amount of sputum, which was foul and occasionally bloody, a loss of 10 pounds (4.5 Kg) in weight, fever (101.5 F), general malaise and weakness. Two weeks before his readmission he mentioned that he had expectorated a "piece of skin" which was "smooth on one side and pussy on the other," and hydatid disease was then suspected for the first time. Further questioning revealed that in January 1929 he had first coughed up "a piece of skin which was very thin, like the inside of an egg shell, and twice the size of one's thumbnail." At intervals of from one to three months he had coughed up these pieces of "skin," which gradually became larger and thicker. They were raised unexpectedly and were not preceded by a paroxysm of coughing.



Fig 4 (case 2)—Frontal and lateral roentgenograms (Oct 16, 1931) showing area of density in the upper lobe of the left lung and in the region of the superior portion of the interlobar fissure

Examination—The results of physical examination were essentially negative except for an area of dullness between the third and the sixth rib in the left anterior axillary line. On roentgenologic examination (fig 4) a diffuse, somewhat homogeneous area of increased density, which was slightly nodular at its upper margin, was seen anteriorly, extending from the first rib to the third intercostal space. The sputum did not contain tubercle bacilli or hooklets. The complement fixation test for *Echinococcus* gave negative results.

Second Operation—Removal of *Echinococcus* Cyst in Upper Lobe of Left Lung (Oct 19, 1931). The axillary portion of the third rib was removed. The pleurae were adherent, and exploratory puncture produced heavy, whitish yellow material at a depth of 1 cm in the lung. The thickened pleura and lung were widely opened with the actual cautery, and immediately cyst membranes began to bulge. The cyst wall was very friable, and all the small and large pieces were completely

shelled out. There was no evidence of daughter cysts. The wall of the remaining cavity, being formed by the pulmonary tissue, bled moderately, and in various portions of the medial portion of the wall there were bronchial openings of medium size. The pulmonary cavity was wiped with dilute solution of formaldehyde U. S. P. (1:50) and packed with gauze that had been treated with petrolatum. The wound in the thoracic wall was irrigated with the solution of formaldehyde and packed wide open.

Pathologic examination of the cyst wall showed fine laminations, characteristic of echinococcus cysts (fig. 5). The cyst wall was largely necrotic and in part showed leukocytic infiltration. No heads or hooklets were seen.

Course—The postoperative convalescence was uneventful. On October 28, a temporary interruption of the left phrenic nerve was made to aid in closure of the

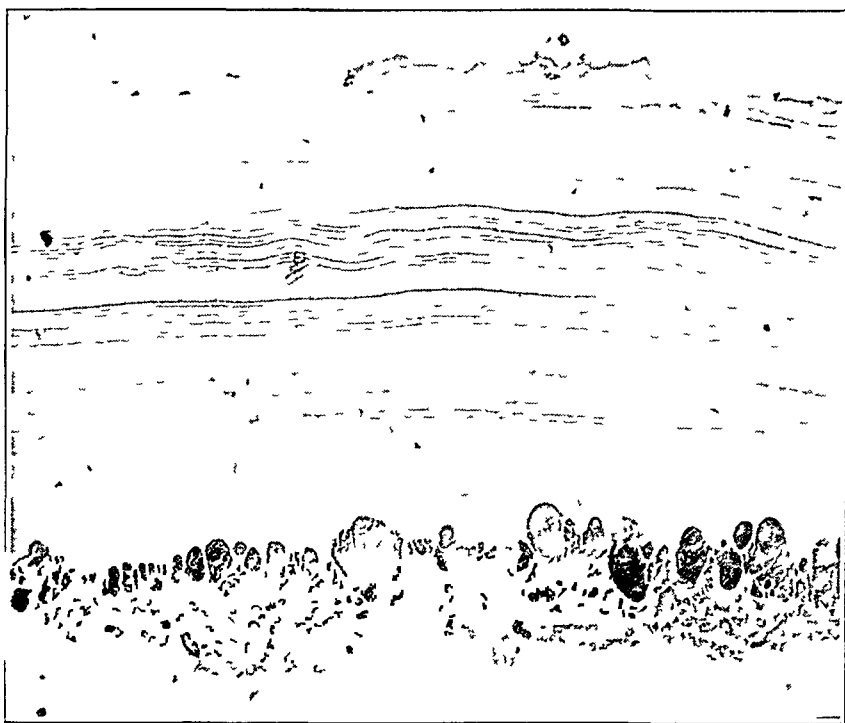


Fig. 5 (case 2)—Photomicrograph showing typical laminated wall of an echinococcus cyst ($\times 33$)

pulmonary defect. The patient was discharged from the hospital November 28, at which time there remained a bronchial fistula, which closed spontaneously two weeks later. Since closure of the fistula there has been no cough or sputum. The patient returned to work on Jan. 10, 1932. Periodic examination since operation has not revealed any evidence of recurrence. He continues to feel well, and there is no cough or expectoration. Roentgenologic examination on Nov. 26, 1937 (fig. 6) showed scattered areas of pleural and pulmonary fibrosis, which were identical with similar areas seen in roentgenograms made in 1932 and 1933.

CASES REPORTED IN THE RECENT LITERATURE

The following cases of hydatid cysts of the lung have been reported since the publication, in 1930, of Phillips' collected series. The dates in parentheses are those on which the report was made.

JOHNS'S CASE⁴ (1930) —A Virginian who had been in the World War for two years returned with the complaint of considerable loss of weight. A "tumor" of the right lung was seen in roentgenograms, and at operation a calcified cyst, about the size of an orange, was removed. The diagnosis was uncertain. About one year later an infection developed in the pleura, and the diagnosis was then confirmed by the finding of hooklets. After excision of the involved pleura the patient made a complete recovery.

It appears likely that the disease in Johns's case developed while the patient was residing in this country, and prior to the two years spent in the World War. This deduction is based on several premises. One is the prevalence of echinococcus disease in domestic animals in Virginia. In 1917, Johnston and Willis¹⁰ reported the occurrence of several epidemics among hogs in Virginia from 1913 to 1914, and they mentioned infestation of 25 per cent of 60 hogs shipped from Charlotte County in November 1917. Also, the latent period before

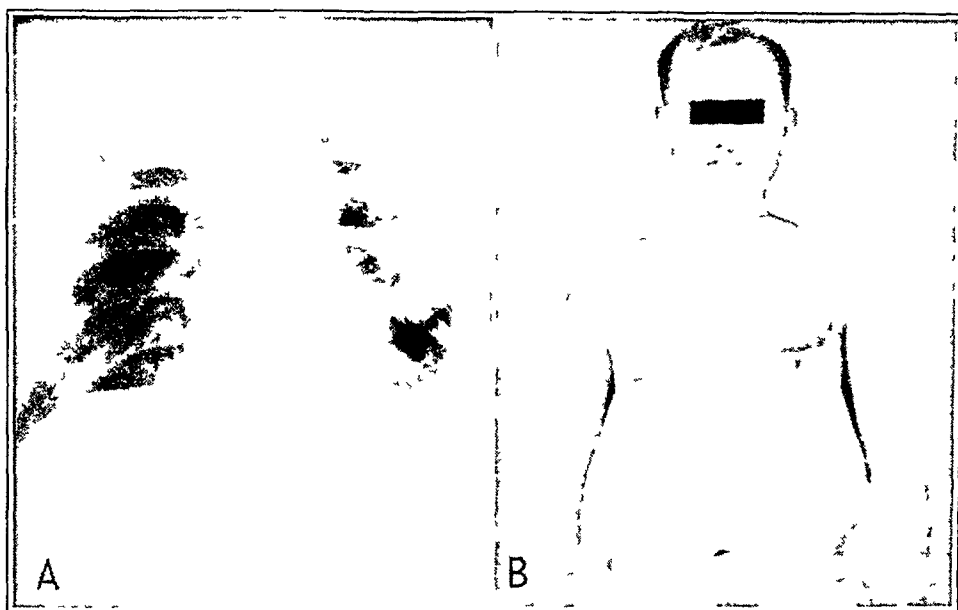


Fig 6 (case 2) —*A*, roentgenogram taken six years after operation, showing no evidence of recurrence of cysts. *B*, photograph of patient. The cyst was removed through the upper incision (healed). The lower inframammary incision was the site of the "negative" exploration in 1928.

the development of symptoms is notably long in many cases of echinococcus disease, and the finding of a calcified cyst in this case suggests that the latent period was longer than the two years of the patient's service in the World War.

LILIENTHAL'S CASE¹¹ (1930) —In the discussion of Phillips' paper, Lilienthal merely stated that he had had 1 case of hydatid cysts of the lung, in which the patient was born in Greece and left there when he was very young. Lilienthal mentioned another case, one of a possible retrosternal hydatid cyst, which is not included with the collected cases presented in this article because the diagnosis was uncertain and the location was neither in the lungs nor in the pleura.

10 Johnston, G. B., and Willis, M. Hydatid Cyst of the Liver with Report of Two Cases, *Surg., Gynec. & Obst.* **25** 101-103 (July) 1917.

11 Lilienthal, H., in discussion on Phillips.¹

ZOHLEN'S CASE¹² (1930) —The case was one of echinococcus cysts of the abdomen and lung in a 46 year old Greek who had come to this country at the age of 25. At the age of 41 he had had an operation for tumors of the abdomen in which, he stated, "the doctor drew water off the tumors." At operation, Zohlen found three cystic tumors in the abdomen. Numerous daughter cysts were removed from the cysts. Pathologic examination revealed that the wall of the cyst was typically laminated, but no hooklets were seen. No attempt was made to aspirate or to remove the cyst from the right side of the chest, and accordingly the diagnosis of the thoracic lesion was not verified.

Roentgenograms of the chest which are reproduced in Zohlen's article show changes consistent with hydatid disease, and in view of the abdominal cysts, it must be assumed that such a diagnosis is the most likely.

HEUER AND ANDRUS' CASE¹³ (1930) —These authors observed 2 instances of hydatid cyst of the liver and "one of pleural or rather parapleural cyst." No details of this case were given.

GRAHAM, SINGER AND BALLON'S CASE¹⁴ (1935) —A man aged 39, who had been a butcher for four years previous to the onset of his illness, and who during the four years immediately preceding this period had been in contact with dead dogs, sheep and other animals in England, complained of cough, dyspnea and expectoration of "pinkish" material of twelve years' duration. A portion of the left ninth rib was resected in 1923, and a typical echinococcus cyst of the pleura, which communicated with similar processes in the lung, was then discovered. There were many daughter cysts and hooklets in the pleura. The patient was treated for an echinococcus cyst of the liver one year later. The authors stated that the lesion in the liver was undoubtedly the primary one. Reexamination in 1927 showed that the patient was in good health. (This case was included in a report by Andrus¹⁵ in 1935.)

NEUHOF'S CASE¹⁶ (1937) —A child aged 13 years had a pulmonary hydatid cyst of six months' duration. At the onset the diagnosis of bronchopneumonia was made, and pus was obtained on two diagnostic aspirations of material from the chest. Fever, cough and expectoration of purulent material continued. The roentgenogram made on admission for treatment showed a homogeneous shadow with a fluid level. At operation, shortly after admission, an elastic mass in the substance of the lower lobe of the right lung was exposed. It was packed off, and at the second stage, one week later, it was entered. There was a fibrous shell of tissue overlying a cyst within the substance of the lung. The cyst contained purulent fluid, which was evacuated. The collapsed cyst wall could then be removed without difficulty. After its removal there were noted a number of large and small bronchial fistulas. The pathologic report on examination of the

12 Zohlen, J. P. Echinococcus Cysts of Abdomen and Lung. Case Report, Wisconsin M. J. **29** 515-517 (Sept.) 1930.

13 Heuer, G. J., and Andrus, W. DeW., in Lewis, D. Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 5, chap. 5, p. 161.

14 Graham, E. A., Singer, J. J., and Ballon, H. C. Surgical Diseases of the Chest, Philadelphia, Lea & Febiger, 1935, pp. 752-753.

15 Andrus, W. DeW. Report of the Chest Tumor Registry, J. Thoracic Surg. **4** 236-250 (Feb.) 1935.

16 Neuhoef, H. The Free Transplantation of Fat for the Closure of Bronchopulmonary Cavities (Lattice Lung), J. Thoracic Surg. **7** 23-24 (Oct.) 1937.

cyst wall was that of infected echinococcus cyst. The wall of the pulmonary cavity soon became clean and rigid, and the bronchial fistulas persisted. One month after the primary operation, the bronchopulmonary cavity was closed with a free transplant of fat. The patient was reported to be free from symptoms.

LESLIE'S CASE⁵ (1938)—A 7 year old boy, American born of Italian descent, had echinococcus cysts in both lungs. Two years previous to the onset of symptoms he had spent some time on a farm in Italy and while there had had a pet dog. The symptoms were recurrent attacks of fever, with a temperature as high as 105 F, for three weeks, slight, nonproductive cough, mild night sweats, and some loss of weight, there was no hemoptysis. At the onset of symptoms he was confined to bed because of weakness, but he had been up and about for one week before his admission to the hospital. Five months before this he had been ill with pneumonia for two months. A roentgenogram showed a large, circumscribed area of density, apparently due to encapsulated fluid, in the lower lobe of the left lung. In the lower lobe of the right lung an area of density about 2.5 cm in diameter was seen. Thoracentesis was carried out on the left side, because of the impression that the patient had encapsulated empyema. Clear, watery fluid under slight pressure was obtained. It did not contain cells, globulin or hooklets. After the thoracentesis there developed a violent pleural reaction, with toxicity, a temperature of 103 F, pain and friction rub. A roentgenogram at this time showed a large, thick-walled cyst in the left lung, with hydropneumothorax on the left side. The cyst contained only a small amount of fluid. Apparently the contents had escaped into the pleural cavity. The complement fixation test for Echinococcus gave a strongly positive reaction. Thoracotomy, with resection of the eighth rib, was performed. Removal of the cyst and marsupialization of the cavity were found to be impracticable, and simple drainage by tube was established. The tube was removed on the ninth day. The prognosis was considered poor because the cyst had not been removed, because the hydatid fluid (presumably infective) had been disseminated throughout the pleural space and because the lesion in the right lung was presumably another cyst. A roentgenogram made five weeks after operation showed reexpansion of the left lung with definite reduction in the size of the cyst. The cyst in the right lung appeared slightly larger than before. The patient was readmitted to the hospital about two months later because of abdominal pain and vomiting, and operation revealed a perforated gangrenous appendix with generalized peritonitis. The postoperative course was stormy, and the patient died fourteen days after operation. Permission for necropsy was refused. At no time during his illness previous to the appendicitis was there evidence of a lesion in any organ other than the lungs.

Craver and Brinkley's Case¹⁷ (1939)—In an article on aspiration for the diagnosis of suspected bronchogenic carcinoma, the author stated that the diagnosis of echinococcus cyst was made in 1 case.

COMMENT

The nativity of patients in 9 of the 46 reported cases of echinococcus cysts of the lung and pleura is not known. In 32 of the reported cases the patients had emigrated to North America. In 5 instances the disease occurred in persons born in the United States. The patient in Garrett's

17 Craver, L. F., and Brinkley, J. S. Aspiration Biopsy of Tumors of the Lung, *J. Thoracic Surg.* 8: 436-461 (April) 1939.

case,² a Negro woman aged 46, a native of Maryland and an inmate of the state asylum for about seventeen years, had apparently never traveled outside this country, the diagnosis was definitely established in this case by the demonstration of hooklets. In Phillips' case 1 the patient had never been outside the state of New York. Although the

Nativity of Patients in Cases of Hydatid Cysts Reported in North America

Author	Date Reported	Nativity of Patient
Gay	1858	Not mentioned
Stille	1858	Not mentioned
Smith, F. G.	1858	Not mentioned
Minot	1859	Not mentioned
Loomis	1879	Ireland
Ainsworth	1880	Poland
Fenger and Hollister	1881	Italy
Smith, D. F.	1882	Not mentioned
Bernay	1882	England
Black	1882	England
Ferguson	1893	Not mentioned
Keyes and Busch	1896	Germany
Beck	1898	Austria
Chown	1901	Iceland
Gay	1901	Italy
Stone	1903	Armenia
Gurlee	1905	Italy
Senn	1905	Greece
Garrett	1906	United States
Smith and Harrington	1907	Russia
MacDonald	1913	New Zealand
Ramey and Emerson	1915	Greece
Davis and Balboni	1917	Italy
Clarkson (case 1)	1917	Macedonia
Clarkson (case 2)	1917	Italy
Crow	1918	Spain
Magath	1921	United States
Balboni (case 1)	1922	Greece
Balboni (case 2)	1922	Greece
Mills	1922	France
Glassman	1922	Siberia
Curran and Locke	1924	Syria
Campbell	1925*	Russia
Ortenberg †	1929	Russia
Phillips (case 1)	1930	United States
Phillips (case 2)	1930	Italy
Johns	1930	United States
Lilienthal	1930	Greece
Zohlen	1930	Greece
Heuer and Andrus	1930	Not mentioned
Graham, Ballou and Singer	1935	England
Neuhof	1937	Not mentioned
Leslie	1938	United States
Craver and Brinkley	1939	Not mentioned
Haight and Alexander	1939	Greece
Haight and Alexander	1939	Denmark

* References to the cases reported up to this date and the nativity of the patients are given in the article by Phillips¹

† The reference to Ortenberg's case is given by Phillips¹. The nativity of the patient in this case is mentioned by Young (Canad. M. A. J. 13: 48, 1923)

remaining 3 native-born patients had traveled outside the United States, it is probable that 1 of these patients (Johns's case) had contracted the disease in this country. The patient reported on by Magath³ was born in the United States and had lived in Nebraska, but had traveled in the Philippine Islands in 1908. In this case, as well as in Leslie's case, it cannot be stated whether or not the disease originated while the patient was in this country, it is possible that infestation may have occurred during residence elsewhere.

During the past twelve years, 6 patients with verified echinococcus disease of the abdominal cavity have been treated in the University Hospital. The country of birth of these patients is as follows: Greece, 2; China, Austria, Bulgaria and Russia, 1 each. All of the patients had hepatic cysts. One also had cysts in the gastrocolic omentum and the pelvis, and another, cysts of the abdominal cavity, pelvis and abdominal wall. The involvement of the abdominal wall had undoubtedly resulted from an operation fifteen years previously. Another patient, an Italian, who refused operation and the diagnosis of whose condition was not verified, presented a calcified cyst of the liver, the complement fixation test for echinococcus disease gave a doubtful positive reaction, but the antigen used was at least one year old.

It is of interest that the reports of cases of echinococcus disease in native-born North Americans continue to be rare, especially in view of the presence of hydatid disease in domestic animals. In 1930, Phillips quoted a personal communication from Maurice C. Hall, chief of the Zoological Division, Bureau of Animal Industry, United States Department of Agriculture, Washington, D. C. Hall reported that figures regarding the incidence of hydatid disease in domesticated animals in this country are not available, and added:

In general, it may be said that hydatids are not generally distributed throughout the United States and that they have a patchy distribution, not well known. They are said to be prevalent in parts of New Mexico, Oklahoma and Arkansas; we can always obtain them on rather short notice from our inspection service at Richmond, Virginia; they are found from time to time at various abattoirs. In 1927, Morris reported that hydatids occurred in 5 per cent of swine at Baton Rouge, and that the former incidence was 20 per cent. Dr. Jalen, our inspector at Cincinnati, Ohio, reported in 1927 that less than 1 per cent of swine at that station were affected.

In more recent personal communications (Aug. 13 and 19, 1936) from Benjamin Schwartz, chief of the Zoological Division, Bureau of Animal Industry, a similar situation was reported. Schwartz stated:

During the fiscal year ended June 30, 1936, 1,513 cattle livers and 21 calf livers were condemned on account of infestation with *Echinococcus*. *Echinococcus* infestation is not rare in swine in certain sections of the United States, particularly in the South. We have no difficulty in securing such material from abattoirs in Richmond, Va. We have been informed recently that *Echinococcus* in the liver of swine is fairly common in abattoirs in Nashville, Tenn.

A personal communication (Oct. 3, 1933) from C. H. Clark, state veterinarian, Department of Agriculture, Lansing, Mich., stated:

To my knowledge, no special investigations have been made in this state regarding the incidence of echinococcus disease in sheep, dogs or other domestic animals. I have never had the opportunity of seeing it in Michigan.

SUMMARY

Two cases of echinococcus disease of the lungs are presented, and the nativity of the patients in the 46 cases of hydatid disease of the lungs and pleura reported in the North American literature is reviewed. The disease has occurred in only 5 persons known to have been born in North America. Certain epidemiologic aspects of the prevalence of hydatid disease in domestic animals in this country are mentioned.

THE COLLOIDAL GOLD REACTION OF BLOOD SERUM IN DISEASES OF THE LIVER

SEYMOUR J GRAY, MD

CHICAGO

The purpose of this paper is to report studies of the colloidal gold reaction of blood serum in diseases of the liver. Zsigmondy,¹ in 1901, laid the foundation for the diagnostic use of the colloidal gold reaction by observing² that "certain colloids, especially proteins," prevented the precipitation of colloidal gold suspensions by electrolytes, each protein exerting a specific degree of protection against precipitation. On the other hand, Lange,² in 1912, found that proteins within certain dilutions did not prevent but actually caused the precipitation.

The mechanism of the colloidal gold reaction has been the subject of much investigation. Numerous workers, including Felton,³ Weston,⁴ Cruickshank⁵ and others,⁶ have shown that the globulin content is the determining factor in the precipitation of colloidal gold and that albumin protects the colloidal suspension from precipitation. The varying colloidal gold curves obtained with spinal fluids in different pathologic conditions result from variations in the balance between the precipitating activity of the globulin and the protective action of the albumin. There is evidence, moreover, that the individual globulin fractions, particularly

From the Department of Medicine of the School of Medicine of the Division of Biological Sciences, the University of Chicago

1 Zsigmondy, R. Die hochrothe Goldlösung als Reagens auf Colloide, *Ztschr f. anal. Chem* **40** 697, 1901

2 Lange, C. Die Ausflockung von Goldsol durch Liquor cerebrospinalis, *Berl. klin. Wchnschr* **49** 897, 1912, Die Ausflockung kolloidalen Goldes durch Cerebrospinalflüssigkeit beiluetischen Affektionen des Zentralnervensystem, *Ztschr f. Chemotherapie* **1** 44, 1912

3 Felton, L. D. Cerebrospinal Fluid and the Colloidal Gold Reaction, *New York State J. Med* **105** 1170, 1917, A Study of the Specificity of the Colloidal Gold Reaction from the Physicochemical Standpoint, *Tr. Sect. Path. & Physiol.*, A. M. A., 1917, p. 73

4 Weston, P. G. The Colloidal Gold Reaction, *Am. J. Syph.* **3** 266, 1919, The Nature of the Substance Causing the Colloidal Gold Reaction, *Am. J. Insan.* **76** 393, 1920

5 Cruickshank, J. The Value and Mechanism of the Colloidal Gold Test, *Brit. J. Exper. Path.* **1** 71, 1920

6 (a) Vogel, K. M. The Nature and Interpretation of the Colloidal Gold Reaction, *Arch. Int. Med.* **22** 496 (Oct.) 1918. (b) Mayr, J. K. Zur Theorie und Praxis der Kolloidreaktionen mit besonderer Berücksichtigung der Goldsolreaktion, *Arch. f. Dermat. u. Syph.* **144** 200, 1923

the euglobulins, play an important role in the precipitation of colloidal gold. Kafka and Samson⁷ and Haug⁸ concluded that the reaction depends primarily not on the quantitative increase in globulin but on the qualitative alteration in the globulin fractions. Reznikoff⁹ reproduced different colloidal gold curves by varying the relative concentrations of the euglobulin, pseudoglobulin and albumin. Fischer¹⁰ expressed the belief that the euglobulin and pseudoglobulin fractions have the strongest precipitating action on colloidal gold solutions. Mellanby and Anwyl-Davies,¹¹ Reznikoff⁹ and Spiegel-Adolph¹² observed that the euglobulin fraction exerts a considerable influence on precipitation.

The present studies of the colloidal gold reaction of blood serum in hepatic disease were instigated by observations that alterations in the plasma proteins,¹³ particularly in the euglobulin fraction,¹¹ are frequently

7 Kafka, V, and Samson, K. Die Eiweissrelation des Liquor cerebrospinalis. Eiweissrelation und Kolloidreaktionen, *Ztschr f d ges Neurol* **117** 128, 1928.

8 Haug, K. Untersuchung zur Frage der Beziehungen zwischen Goldsolreaktion, Zellgehalt, und Eiweissrelation nach Kafka im Liquor cerebrospinalis, *Ztschr f d ges Neurol u Psychiat* **149** 103, 1933.

9 Reznikoff, P. The Action of Proteins and Blood Serum on Colloidal Gold Solutions and Its Quantitative Interpretation, *J Lab & Clin Med* **8** 92, 1922.

10 Fischer, H. Ueber den Mechanismus der Goldsolreaktion im Liquor cerebrospinalis, *Ztschr f d ges exper Med* **14** 60, 1921.

11 Mellanby, J, and Anwyl-Davies, T. The Precipitation of Colloidal Gold by Cerebrospinal Fluid. The Diagnosis of Neurosyphilis, *Brit J Exper Path* **4** 132, 1923.

12 Spiegel-Adolph, M. Physikalisch-chemische Untersuchungen bestrahlter Proteine. Die Veränderungen des Serumalbumins bei Ultraviolettbestrahlung und ihre Beziehungen zur Hitzegerinnung, *Biochem Ztschr* **186** 181, 1927.

13 (a) Grenet, H. Diminution des albumines du sérum sanguin chez les hépatiques, *Compt rend Soc de biol* **63** 552, 1907. (b) Gilbert, A, and Chiray, M. Diminution des substances albumineuses du sérum sanguin chez les cirrhotiques ascitiques, *ibid* **63** 487, 1907. (c) Felinski, W. L'augmentation de taux de la globuline dans le serum du sang, *Presse méd* **20** 236, 1922. (d) Abram, P, and Wallich, R. Modifications du serum sanguin au cours des cirrhoses du foie avec ascites. Inversion du rapport serum-globulines, *Compt rend Soc de biol* **101** 291, 1929. (e) Snell, A. M. Changes in Proteins of Blood in Hepatic Disease, *Proc Staff Meet, Mayo Clin* **10** 489, 1935. (f) Myers, W. K, and Keefer, C. S. Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, *Arch Int Med* **55** 349 (March) 1935. (g) Foley, E. F, Keeton, R. W, Kendrick, A. B, and Darling, D. Alterations in Serum Proteins as an Index of Hepatic Failure, *ibid* **60** 64 (July) 1937. (h) Tumen, H, and Bockus, H. L. The Clinical Significance of Serum Proteins in Hepatic Disease, *Am J M Sc* **193** 788, 1937.

14 (a) Gios, W. Zur Frage gesetzmässiger Veränderungen des Blut-eiweissbildes beim multiplen Myelom, *Deutsches Arch f klin Med* **177** 461, 1935.

associated with diseases of the liver, and by the fact that the euglobulin fraction has been shown to play an important role in colloidal gold precipitation¹⁵

The colloidal gold reaction of the blood serum was studied in 96 cases of diseases of the liver: 46 cases of cirrhosis, 14 of acute parenchymatous disease, 25 of neoplastic involvement and 11 of miscellaneous diseases. The diagnoses were confirmed by autopsy, biopsy or laparotomy in 11 cases in the first group, 2 in the second, 13 in the third and 8 in the fourth. A control series and a series of 20 cases of syphilis without clinical evidence of liver disease were studied also. The control series included 95 patients. Twenty of these were normal adults, and 75 had various extrahepatic diseases. Normal livers were found at autopsy, biopsy or laparotomy in 22 patients.

In addition to the colloidal gold tests, the chemical studies of the blood included determinations of the plasma albumin, globulin, cholesterol, cholesterol esters and fibrinogen. The Takata-Ara, bromsulphalein retention, and galactose tolerance tests and other tests of hepatic function were also carried out in many cases.

METHODS

The colloidal gold solution is prepared and acidified in accordance with Klaas's modification of Patterson's¹⁶ method, as used routinely in the serology laboratory of the University of Chicago Clinics. The amount of fiftieth-normal hydrochloric acid to be added to the colloidal gold solution is determined with alizarin red as indicator and is checked further by control tests with serums from normal persons and with "known positive" serums from patients known to have hepatic disease. The sensitivity of the reaction may be increased or decreased by increasing or decreasing the acidity of the solution. Standardization need be done only once for each supply of colloidal gold prepared, since several liters may be kept for as long as two months without changing the acid requirement. Immediately before each test is performed acid is added drop by drop, the solution being constantly agitated. Usually from 11 to 17 cc of fiftieth-normal hydrochloric acid is needed for every 50 cc of colloidal gold used. The pH is usually about 7, varying with the individual colloidal gold preparation.

Immaculately clean pyrex glassware should be used throughout the procedure.

(b) Kendall, F. E. Studies on Serum Proteins. I. Identification of a Single Serum Globulin by Immunological Means, Its Distribution in the Sera of Normal Individuals and of Patients with Cirrhosis of the Liver and with Chronic Glomerulonephritis, *J. Clin. Investigation* **16** 921, 1937. (c) de Vries, A. On the Connection Between the Takata-Jezler Reaction and Its Variant, the Mancke-Sommer Reaction, and the Globulin Fractions of the Blood, *Acta med. Scandinav.* **98** 95, 1938.

¹⁵ Reznikoff⁹, Fischer¹⁰, Mellanby and Anwyl-Davies¹¹, Spiegel-Adolph¹².

¹⁶ Patterson, J. Preparation of Colloidal Gold, *Brit. J. Exper. Path.* **12** 143, 1931.

Five cubic centimeters of venous blood is obtained from the patient before breakfast and centrifuged, 0.1 cc of clear serum is removed and diluted 1:350 with physiologic solution of sodium chloride. In the first of a series of ten tubes is placed 1.8 cc of a 0.3 per cent solution of sodium chloride. In each of the following nine tubes is placed 1 cc of a 0.3 per cent solution of sodium chloride. Then 0.2 cc of the diluted serum is added to the first tube of the series. The contents are mixed, and 1 cc is then transferred to the second tube and mixed. This procedure is followed throughout the series of ten tubes, and 1 cc of the mixture in the last tube is discarded. Five cubic centimeters of acidified colloidal gold solution is added to each tube, and the readings are made after twelve to twenty-four hours.

In reading the test the same numbers are used as in reading the regular Lange reaction: 0, red; 1, red-blue; 2, orchid; 3, blue; 4, light blue; 5, colorless.

The greater the precipitation of the colloidal gold, the higher the numbers, 5 represents complete precipitation. The normal range in our experiments varied from 0000000000 to 3332210000. The number 3 appears only occasionally on the left side of the curve. The positive reaction is similar to the dementia paralytica type of curve obtained with spinal fluid—for example, 5532100000 or 5432100000.

RESULTS

Cirrhosis of the Liver—The colloidal gold reaction of the serum was positive in all 46 cases of cirrhosis of the liver. The type and severity of the disease varied. The diagnosis was confirmed by autopsy or biopsy in 11 cases (table 1).

The plasma proteins were studied in 39 of the 46 cases in this group. The globulin was increased to an average of 3.19 Gm per hundred cubic centimeters (normal range 1.5 to 2.8 Gm). Increased values were noted in 23 cases, more frequently in advanced hepatic disease than in early cirrhosis. A decrease in albumin was observed in 26 cases, with an average value of 3.50 Gm for the group (normal range 4 to 6 Gm). Low plasma albumin values were associated more closely with the severity and duration of the hepatic disease than with the presence of ascites. Increases in globulin compensated for the decrease in albumin in all but 9 cases, so that the average value of the total plasma proteins was within normal limits (6 to 8 Gm). Abnormally low or inverted albumin-globulin ratios were found in 28 cases, this fact is in accord with the numerous observations¹³ on the frequency of variation of the plasma protein content in hepatic diseases. Although positive colloidal gold reactions were associated in a considerable number of cases with abnormal plasma protein values, they were also obtained for 16 plasmas with normal globulin concentrations, and for 11 with normal albumin-globulin ratios.

The total plasma cholesterol, determined in 39 cases, was normal (140 to 200 mg per hundred cubic centimeters) in 20, increased in 7 and decreased in 12 cases in which severe hepatic damage was predominant. The plasma cholesterol esters, determined in 36 cases, were

TABLE 1—Data on the Blood in Cirrhosis of the Liver

Case No	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/Globulin, Gm per 100 Cc	Plasma Fibrinogen, Gm per 100 Cc	Plasma Cholesterol/Esters, Mg per 100 Cc	Wassermann Test	Takata Ara Test	Van den Bergh Reaction and Icteric Index	Galactose Tolerance, Bromsulphalein Retention and Other Tests	Diagnosis
1	W Z	5545310000	3.54/4.21		163/79	Neg		Direct—faint delayed Indirect—normal Icteric index .63	Gal tol —1.3 Gm Brom —60 per cent	Portal cirrhosis
2	B F	55533210000				Neg				Portal cirrhosis with ascites
3	A R	4322000000	2.22/2.97		227/	Neg				Portal cirrhosis (autopsy)
4	H J	5553210000	3.74/2.29	0.24	150/55	Neg	Neg		Gal tol —2.5 Gm Brom —2 per cent Levulose tol —normal	Portal cirrhosis (autopsy)
5	P M	5553210000	2.53/4.25	0.21	150/44	Neg	Pos	Icteric index .17		Portal cirrhosis with ascites
6	A T	2552110000	2.50/3.25	0.39	123/33	4+	Pos	Direct—negative Indirect—normal		Portal cirrhosis with ascites
7	H P	1553210000	3.31/3.07		126/17	Neg	Pos	Icteric index .25		Portal cirrhosis with ascites
8	J F	5555442100	4.46/3.95	0.53	133/38	4+	Pos	Direct—negative Indirect—normal	Brom —5 per cent	Portal cirrhosis with ascites
9	A B	5532100000	4.22/2.17	0.21	132/	2+		Indirect—normal Icteric index .83		Portal cirrhosis and syphilis
10	F H	4453210000			203/122	Neg	Pos			Portal cirrhosis
11	F M	5521100000	2.87/2.84		138/41	Neg	Pos			Portal cirrhosis
12	E S	5555321000	2.06/3.65		176/78	Neg	Neg	Indirect—normal		Portal cirrhosis with ascites
13	V S	5543210000				2+	Pos	Indirect—normal		Portal cirrhosis with ascites
14	P T	5543100000	2.62/5.06		160/70	Neg	Pos	Indirect—normal		Portal cirrhosis (autopsy)
15	M K	5553210000	3.96/2.53		167/too low to measure	Neg	Pos	Indirect—7.1 mg per 100 cc Icteric index .60		Portal cirrhosis
16	B B	4322000000	3.01/2.88		167/41	Neg	Pos	Indirect—6.2 mg per 100 cc Icteric index .50		Portal cirrhosis with ascites
17	J H	5542110000	2.97/4.55		140/56	Neg	Pos	Indirect—normal		Portal cirrhosis
18	M C	5321000000	2.49/3.43		155/53	Neg	Neg	Indirect—normal		Portal cirrhosis
19	A W	5453210000	4.12/2.45		357/285	Neg	Pos	Icteric index .16	Gal tot —2.1 Gm	Portal cirrhosis with esophageal varices
20	P R	4533210000	4.02/3.32		154/47	Neg	Pos	Indirect—normal		Portal cirrhosis
21	L F	4455310000	3.42/3.69		150/70	Neg	Pos	Indirect—1.0 mg per 100 cc		Portal cirrhosis
22	A W	5453210000				Neg				Portal cirrhosis
23	P C	4421100000	4.15/1.35		155/77	Neg	Pos			Portal cirrhosis with esophageal varices

24	S R	2533100000	3 68/4 18			218/90	Neg		Portal cirrhosis, macrocytic anemia
25	O W	1533210000	2 54/3 10			156/47	Neg		Portal cirrhosis with ascites
26	W W	4542431000	3 75/3 28			162/48	Neg		Portal cirrhosis with ascites
27	A V	5554321000	3 60/1 96			125/ 5 5	Neg	Icteric index 53 Indirect—0.85 mg per 100 cc	Portal cirrhosis
28	J B	5555321000	3 03/4 03	0 30		155/63	4+		Portal cirrhosis with ascites
29	P C	5555310000	5 09/3 67			120/ too low to read	Neg		Portal cirrhosis
30	M W	5554321000	1 38/2 89			298/170	Neg	Indirect—normal	Portal cirrhosis (biopsy)
31	L F	5553321000	4 76/2 52	0 27		151/60	Neg	Indirect—4 mg per 100 cc	Early cirrhosis of liver (biopsy), macrocytic anemia, splenomegaly
32	L W	1332100000	3 79/2 81			169/95	Neg	Indirect—normal	Subcapsular cirrhosis (autopsy)
33	B H	5554210000					Neg		Cardiac cirrhosis, large, hard, pulsating liver, ascites
34	A D	4522100000	4 33/2 80				Neg		Cardiac cirrhosis large hard liver, cardiac failure
35	K R	5554210000	3 14/3 66			137/59	Neg		Cardiac cirrhosis, large, hard, nodular liver with ascites
36	A A	5543210000	3 91/2 87			160/60	4+		Cardiac cirrhosis tricuspid regurgitation, large, hard, nodular liver with ascites
37	F L	5321000000					Neg		Cardiac cirrhosis (autopsy)
38	A S	5543100000	3 93/3 02	0 37		147/52	Neg	Direct—neg Indirect—normal	Cardiac cirrhosis with ascites (biopsy)
39	I B	5555321000	3 61/2 96			120/40	Neg		Cardiac cirrhosis, tricuspid regurgitation, large, hard, nodular liver
40	M S	5555321000					Neg		Cardiac cirrhosis, tricuspid regurgitation, large, hard, nodular liver
41	D L	1543210000	4 16/2 70			160/53	Neg	Indirect—normal	Cardiac cirrhosis heart failure, large, hard liver with ascites
42	B J	5554320000	2 33/5 09			138/48	Neg	Indirect—1.1 mg per 100 cc	Hemochromatosis with cirrhosis of the liver (autopsy)
43	J P	5542100000	2 49/3 80	0 23		121/ 5 4	Neg	Biphasic—5 mg per 100 cc	Biliary cirrhosis (autopsy)
44	A E	5555310000	4 16/3 18			357/80	Neg	Icteric index 80	Biliary cirrhosis
45	J L	0443210000	2 96/2 60			302/	Neg	Icteric index 82	Biliary cirrhosis (autopsy)
46	L A	1433100000	4 14/1 65	0 27		88/39	Neg	Icteric index 15	Atrophic cirrhosis with esophageal varices

normal (40 to 70 per cent of the total plasma cholesterol) in 14 cases and decreased in 22 cases of extensive involvement of the liver, in 2 of the latter the amount of esters was too low to determine. Better results were obtained with the Takata-Ara test in this group of cases than in any other group in our study, for 28 of the 35 tests performed were positive.

Acute Parenchymatous Hepatic Disease—Positive colloidal gold reactions were obtained in 13 of 14 cases of acute parenchymatous disease of the liver (table 2). The single negative reaction observed was in the case of a 30 year old man with the clinical diagnosis of catarrhal jaundice, whose symptoms were subsiding when the test was made (table 2, case 5). The plasma proteins were determined in 10 of the 14 cases in this group. The globulin was increased to an average of 3.16 Gm per hundred cubic centimeters. It is interesting that there were 6 cases with increased globulin, and that the average globulin values in acute parenchymatous disease of the liver and those in hepatic cirrhosis approximated each other closely. However, in contrast to the low albumin values found in hepatic cirrhosis, the albumin values in the parenchymatous diseases maintained a normal average of 4.38 Gm and were abnormally low in only 2 instances. Total plasma proteins were normal in every case, with an average of 7.54 Gm, and were consistently higher than in the cases of cirrhosis of the liver. Positive colloidal gold reactions were again obtained in the presence of both abnormal and normal albumin globulin ratios—4 cases of the former and 6 of the latter.

The changes in the plasma cholesterol and cholesterol esters in this group were somewhat similar to those found in the cases of hepatic cirrhosis. The total plasma cholesterol was determined in 13 of the 14 cases and was found normal in 6, increased in 5 and decreased in 2. The plasma cholesterol esters, determined in 12 cases, were normal in 3 and decreased in 9, in 2 of these the quantity was too small to determine. The Takata-Ara reaction was considerably less sensitive than in the first group of cases, with only 3 positive tests among the 8 carried out.

Neoplastic Involvement of the Liver—There were 25 cases of neoplastic disease of the liver, in which the diagnosis was confirmed in 13 instances by autopsy, biopsy or laparotomy. Positive colloidal gold reactions were obtained in 19 (table 3). In 4 of the 6 cases in which the reaction was negative there was minimal hepatic involvement, a few small carcinomatous nodules being found at autopsy. The plasma globulin, which averaged 3.10 Gm per hundred cubic centimeters, was increased in 9 cases, whereas the plasma albumin averaged 3.73 Gm and was decreased in 10 of the 17 cases studied. Since the increase in globulin compensated for the decrease in albumin, the total plasma

TABLE 2—Data on the Blood in Acute Parenchymatous Disease of the Liver

Case No	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/Globulin, Gm per 100 Cc	Plasma Cholesterol/Cholesterol Esters, Mg per 100 Cc	Takata Ara Test	Van den Bergh Reaction and Icteric Index	Galactose Tolerance, Bromsulphalein Retention and Other Tests	Diagnosis
1	R S	5543110000	4 68/2 53	185/67	Neg	Icteric index 40	Gal tol —5 6 Gm	Catarrhal jaundice
2	P C	5543210000	5 81/2 90	232/50	Pos	Icteric index 83	Gal tol —4 4 Gm	Catarrhal jaundice
3	F I	5553210000	4 47/2 22	333/125	Neg	Icteric index 46		Catarrhal jaundice
4	M H	5532110000		154/33 6	Pos	Icteric index 30		Catarrhal jaundice
5	F W	0211000000		131/		Icteric index 37		Catarrhal jaundice
6	F G	5554000000		181/too low to measure	Pos	Direct—strong biphasic Indirect—4 mg per 100 cc		Catarrhal jaundice
7	L K	5542210000				Indirect—10 mg per 100 cc	Brom —10 per cent	Catarrhal jaundice
8	F B	5532100000	4 23/3 19	177/92		Icteric index 75		Infectious hepatitis (autopsy)
9	F P	5555421000	3 74/3 75	161/63				Toxic hepatitis with jaundice following pneumonia
10	R S	2332110000	4 37/2 01			Icteric index 15		Six weeks later, no symptoms
11	A P	4432110000	4 19/2 84	212/87		Icteric index 60	Gal tol —3 0 Gm	Arsenical hepatitis
12	L B	4543100000	3 97/5 03	201/41 2	Neg	Icteric index 65	Gal tol —6 4 Gm	Arsenical hepatitis
13	P V	4533210000	4 33/3 35	241/65	Neg	Icteric index 50		Arsenical hepatitis
		4444310000	5 16/1 87	238/90	Neg	Icteric index 49	Benzoc acid—1 62 Gm	Cinchophen poisoning of liver
14	A N	5555431000	3 28/5 04	119/not readable		Direct—immediate, indirect—10 mg per 100 cc		Infectious hepatitis (autopsy)

TABLE 3—Data on the Blood in Neoplastic Diseases of the Liver

Case No	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/ Globulin, Gm per 100 Cc	Plasma Fibrinogen, Gm per 100 Cc	Plasma Cholesterol/ Cholesterol Esters, Mg per 100 Cc	Takata-Ara Test	Van den Bergh Reaction and Icteric Index	Primary Source of Tumor
1	L M	4492110000	3 59/2 44	0 31	140/49	Neg	Indirect—normal	Carcinoma of stomach with metastases to liver (laparotomy)
2	S U	4553320000	4 50/2 72		172/70			Carcinoma of stomach with metastases to liver (laparotomy)
3	P M	0233210000	4 21/2 49		127/63	Neg	Indirect—normal	Carcinoma of stomach with a few small metastatic nodules in liver (laparotomy)
4	F F	5532110000						Carcinoma of stomach with metastases to liver (autopsy)
5	P R	0000100000	3 49/2 62		136/62			Carcinoma of stomach with metastases to liver (laparotomy) bromsulph test normal
6	J S	1543210000	5 52/2 86		212/58	Neg	Icteric index .99	Carcinoma of stomach with metastases to liver
7	B K	5543210000	1 76/4 73		38/80 not readable	Neg	Direct—positive, Indirect—4 7 mg per 100 cc	Carcinoma of stomach with metastases to liver (autopsy)
8	C R	0253310000						Carcinoma of breast with metastases to liver (autopsy)
9	E S	5553210000				Pos	Indirect—normal	Carcinoma of breast with metastases to liver
10	M J	5321000000	4 26/2 44		139/38	Neg	Indirect—4 6 mg per 100 cc	Carcinoma of breast with metastases to liver
11	N S	0042100000				Neg		Primary carcinoma of liver (biopsy)
12	A M	0451621000	3 55/3 07	0 6	185/73	Neg	Indirect—normal	Primary tumor of liver (autopsy)
13	I D	5332100000				Neg		Carcinoma of prostate with metastases to liver and ascites
14	P P	5555321000	2 56/3 98		160/40			Carcinoma of prostate with metastases to liver and ascites
15	C P	1155321000				Neg	Indirect—normal	Carcinoma of rectum with metastases to liver, and ascites
16	D L	5533210000	3 94/2 71	0 87	239/68		Indirect—normal	Carcinoma of prostate with metastases to liver (biopsy)
17	H A	5555431000	6 20/3 50		118/42	Pos	Indirect—normal	Carcinomatosis with involvement of liver
18	J W	5532100000				Neg		Carcinoma of pancreas with metastases to liver
19	A K	0211100000	2 21/3 25				Indirect—5 4 mg per 100 cc	Carcinoma of biliary tract with small amount of infiltration at hilus of liver (autopsy)
20	S H	1333210000					Direct—biphasic, Indirect—8 5 mg per 100 cc	Carcinoma of pancreas with a few small nodules in liver (autopsy)
21	A V	2332210000	3 31/3 53	1 35	111/32			Carcinoma of pancreas with metastases to liver
22	B O	0123211000	4 56/1 49		212/46			Carcinoma of pancreas extending up into hilus of liver (laparotomy) gal tol, 5 8 Gm
23	J L	4543210000	3 50/4 31		180/54	Neg	Icteric index .60	Carcinoma of rectum with metastases to liver
24	F P	5533211000	2 06/3 48	0 25	141/44		Indirect—normal	Carcinoma of rectum with metastases to liver
25	P G	0532210000	4 19/3 15		227/44		Biphasic—strong, Indirect—8 3 mg per 100 cc	Carcinoma of rectum with metastases to liver gal tol, 5 7 Gm

proteins averaged 6.83 Gm per hundred cubic centimeters, and were normal in 14 of the 17 cases studied. The degree of abnormality in the value for plasma protein was directly related to the extent and duration of the neoplastic involvement (table 3, cases 7, 14, 23, 24). As in the other groups of cases, positive colloidal gold reactions did not occur only with abnormal plasma protein values, but were found in conjunction with normal globulin values in 5 instances and with normal albumin-globulin ratios in 4 instances.

The total cholesterol and the cholesterol esters of the plasma were determined in 16 of the 25 cases. The former was normal in 7 cases, high in 4 and low in 5 whereas the latter were normal in 5 cases and low in 11 cases of advanced parenchymal damage. The Takata-Ara test was less sensitive here than in the previous group of cases, yielding only 2 positive reactions in the 12 tests performed.

Miscellaneous Hepatic Diseases—The colloidal gold reaction was positive in each of the 11 cases of miscellaneous hepatic diseases, in which the diagnosis was confirmed by autopsy or laparotomy in 8 cases (table 4). The plasma proteins were studied in 9 of the 11 cases. The globulin, averaging 2.99 Gm per hundred cubic centimeters, was increased in 5 cases. Although the globulin values were less altered in this group than in the cases of other types of hepatic disease studied, the plasma albumin, averaging 3.27 Gm, was sufficiently low to produce abnormal albumin-globulin ratios in 8 of the 9 cases studied. The total plasma proteins, however, averaged 6.26 Gm and were within the lower limits of normal in 6 of the 9 cases studied. Here again the colloidal gold reaction was positive in the 4 cases with normal plasma globulin values and in the 1 case with a normal albumin-globulin ratio.

The plasma cholesterol, determined in 9 cases, was normal in 5, high in 2 and low in 2, whereas the cholesterol esters, studied in 7 cases, were normal in 2 and low in 5. In 2 of these cases the values for the cholesterol esters were too low to determine. The Takata-Ara reaction was positive in 1 of the 3 tests performed.

The Colloidal Gold Reaction of Serum from Normal Persons and from Patients with Various Extrahepatic Diseases—The colloidal gold reaction was studied in a control series of 95 nonsyphilitic persons with no demonstrable disease of the liver. This series included 20 normal adults and 75 patients with extrahepatic diseases, including lobar pneumonia, acute infectious diseases, acute and chronic nephritis, extrahepatic jaundice, blood dyscrasias and neoplasms. The presence of a normal liver was confirmed in 22 of the 75 cases at autopsy, biopsy or laparotomy. The colloidal gold reaction was negative in the serums from the 20 normal adults and in those of 73 of the 75 patients with various extrahepatic diseases. The 2 positive reactions were observed

TABLE 4—Data on the Blood in Miscellaneous Diseases of the Liver

Case No	Patient	Serum Colloidal Gold Reaction	Plasma Albumin, Gm per 100 Cc	Plasma Fibrinogen, Gm per 100 Cc	Plasma Cholesterol/ Esters, Mg per 100 Cc	Takata Ara Test	Van den Bergh and Icteric Index	Galactose Tolerance, Bromsulphalein Retention and Other Tests	Diagnosis
1	O Y	5553210000	4 98/2 41		258/143	Pos	Icteric index .62		Chronic cholecystitis with hepatitis (laparotomy)
2	A II	4543210000	2 06/2 40	0 55	106/200 low to measure			Brom —20 per cent	Abscesses of liver (laparotomy)
3	R C	2433210000	3 31/3 20		176/65				Hodgkin's disease—infiltration of liver (autopsy)
4	B H	4532100000	1 93/2 40						Extreme degree of fatty degeneration of liver (autopsy)
5	E K	5521000000	3 05/2 38		120/200 low to measure		Indirect—10 mg per 100 cc		Considerable fatty degeneration of liver (autopsy)
6	C D	5553421000	2 73/3 08		139/				Considerable fatty degeneration of liver (autopsy)
7	B A	1531000000	3 09/3 01		189/60				Marked fatty degeneration of liver (autopsy)
8	G B	4522110000				Neg		Gal tol —2.7 Gm brom —no ret	Fatty infiltration of liver following diabetes (large, hard, smooth liver)
9	S K	5532110000	4 33/3 33		169/58			Gal tol —0.5 Gm , brom —no ret	Hepatosplenomegaly and anemia
10	B L	5533210000	3 42/4 12	0 65	169/67			Brom —3 per cent, benzoic acid—2.1 Gm	Miliary infectious granuloma of liver (autopsy)
11	W W	5422210000			376/	Neg		Gal tol —2 Gm	Lipoid histiocytosis (large hard liver)

TABLE 5—*Data on Blood in Various Extrahepatic Diseases*

Case No	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/Globulin Gm per 100 Cc	Plasma Cholesterol/Cholesterol Esters, Mg per 100 Cc	Icteric Index	Diagnosis
1	J O	0001200000		212/46	28	Common duct stone liver normal (laparotomy)
2	G W	0123100000	5 57/3 14	313/163	125	Common duct stone, liver normal at operation
3	E B	0210000000	4 36/2 82	208/49	75	Common duct stone liver normal at operation
4	L M	0110000000	5 05/2 89	170/71		Cholelithiasis liver normal at operation
5	C A	0121000000	4 75/2 26		115	Common duct stone, liver normal at operation
6	F S	0001000000	3 96/2 53	202/87	30	Common duct stone liver normal at operation
7	T H	0013210000	4 11/2 86	193/60	41	Cholelithiasis liver normal at operation
8	N P	0211000000	1 90/2 62			Nephrotic nephritis
9	A B	2221000000	1 19/2 73	444/250		Nephrotic nephritis
10	A M	0111100000	4 54/1 72	155/60		Acute nephritis
11	D H	1211000000	1 63/3 31			Chronic glomerulonephritis
12	A L	0000000000	2 90/3 87			Chronic glomerulonephritis, liver normal at autopsy
13	S K	1121000000	4 01/3 33	175/86		Chronic glomerulonephritis
14	A S	2221000000				Chronic glomerulonephritis
15	F G	0111100000	4 75/3 14	174/90		Chronic glomerulonephritis liver normal at autopsy
16	E F	2321000000	3 20/1 89			Chronic glomerulonephritis liver normal at autopsy
17	N G	1111000000	1 32/2 59	265/118		Chronic glomerulonephritis liver normal at autopsy
18	A M	0110000000	3 80/2 72	176/29		Hodgkin's disease liver normal at autopsy
19	B G	0111100000	4 29/1 93	135/54		Hodgkin's disease
20	K R	0110000000	4 22/1 81			Lymphosarcoma (liver normal at autopsy)
21	G S	0110000000				Carcinoma of stomach pneumonia liver normal at autopsy
22	J T	2200000000	3 82/2 52	192/81		Carcinoma of stomach liver normal at autopsy
23	A L	0022100000	3 54/3 12	171/51		Kidney tumor liver normal at autopsy
24	B C	1123210000	3 98/3 58			Carcinoma of lung
25	W D	0122100000	4 84/2 89	177/51	55	Carcinoma of biliary tract liver normal at operation
26	A B	5554310000	3 41/3 53	129/64		Subacute bacterial endocarditis
27	C J	2221000000	4 48/3 05			Subacute bacterial endocarditis
28	A S	0001200000	3 86/3 06	184/83		Coronary occlusion
29	A H	5553210000	2 89/3 34	182/102		Passive congestion of liver from cardiac failure (autopsy)
30	B T	0120000000	4 56/2 46	178/29		Rheumatic heart disease
31	S S	0111100000	2 96/3 46	160/30		Erysipelas
32	O E	0121100000	4 02/3 61	134/53		Acute sinusitis
33	S L	1232100000				Mastoiditis temperature 104 F liver normal at autopsy
34	A F	0110000000				Pulmonary tuberculosis liver normal at autopsy
35	S W	0121100000	5 43/1 28	159/67		Pulmonary tuberculosis liver normal at autopsy
36	A L	0110000000	4 66/2 34			Pernicious anemia
37	B G	0221000000	4 87/2 28	141/55		Pernicious anemia
38	S R	0210000000	5 45/2 04			Duodenal ulcer
39	P N	1123200000	2 98/4 02	206/108		Duodenal ulcer
40	R C	0110000000	4 50/2 06	190/88		Spastic colitis
41	S H	1221100000	4 29/2 17	174/69		Bacillary dysentery
42	S H	0111000000	3 54/2 17	128/49		Hyperthyroidism
43	L G	1100000000	5 16/1 88	143/62		Splenomegaly, liver normal (biopsy)
44	S H	0121000000	4 87/2 88	187/98		Boeck's sarcoid
45	G A	0111000000	4 35/2/21			Multiple myeloma

in a case of subacute bacterial endocarditis and in one of passive congestion of the liver. Data on 45 of the cases of extrahepatic disease are given in table 5.

The values for plasma albumin, globulin, cholesterol and cholesterol esters were found to be within normal limits in the 20 normal adults. Plasma protein determinations in 40 of the 75 cases of extrahepatic disease revealed a normal average value for globulin of 2.70 Gm per hundred cubic centimeters, and a slightly lowered value for albumin, 3.96 Gm. Normal total proteins, averaging 6.66 Gm per hundred cubic centimeters, were present in 35 of the 40 cases. The albumin was diminished in 16 cases, it was markedly decreased in 3 cases of acute

TABLE 6—*Data on Blood Serum in Syphilis*

Case No.	Patient	Serum Colloidal Gold Reaction	Plasma Albumin/Globulin Gm per 100 Cc	Plasma Cholesterol/Cholesterol Esters, Mg per 100 Cc	Wasser mann Reaction	Diagnosis
1	F M	1221100000	4.07/2.17	156/76	3+	Central nervous system syphilis no arsenical therapy
2	F K	5442110000	3.69/3.46	162/42	4+	Central nervous system syphilis arsenical therapy
3	A S	555321000	4.76/2.89	134/58	4+	Central nervous system syphilis arsenical therapy
4	L S	2532110000	3.68/3.44	159/60	4+	Syphilitic heart disease arsenical therapy
5	T M	5521110000	4.17/3.13		4+	Syphilitic heart disease no arsenical therapy
6	B S	1532100000				Syphilitic heart disease no arsenical therapy
7	N M	5552100000	4.85/3.14	175/90	3+	Primary syphilis mild hepatitis from arsenical therapy
8	S L	5321000000				Primary syphilis arsenical therapy
9	L F	1221000000				Secondary syphilis arsenical therapy
10	F M	5521000000				Secondary syphilis arsenical therapy
11	N D	0231000000	3.71/4.02	127/44	4+	Tertiary syphilis splenomegaly liver normal size

nephritis and 3 of chronic nephritis with albuminuria, and was lowered to a lesser degree in 2 cases of heart disease (in 1 of which ascites was present), 2 of infectious diseases, 4 of neoplasm, 1 of hyperthyroidism and 1 of duodenal ulcer. An increase in the plasma globulin was observed in 15 of the 16 cases in which the plasma albumin was decreased. The colloidal gold reaction was negative in 13 of the 15 cases with high globulin values.

The plasma cholesterol was elevated in 4 cases of extrahepatic jaundice and normal in 2, in contrast to the cholesterol values in intrahepatic jaundice, relatively few of which were above normal. The cholesterol esters were normal in 3 cases of jaundice and lowered in 3. In 24 cases of extrahepatic disease without jaundice, the cholesterol was normal in 18, high in 3 and low in 3, whereas the cholesterol esters were normal in 18 cases and lowered in only 6, in contrast to the predominant lowering observed in intrahepatic disease.

Serum Colloidal Gold Reaction in Syphilis—The colloidal gold reaction was positive in 8 and negative in 12 of 20 cases of syphilis with no clinical evidence of hepatic involvement. Data for 11 of these cases are given in table 6. The plasma globulin, averaging 3.17 Gm per hundred cubic centimeters, was increased in 5 of the 7 cases in which proteins were determined, and the colloidal gold reaction was positive

TABLE 7—*Comparison of Colloidal Gold Reaction of Blood Serum and of Spinal Fluid*

Case No	Colloidal Gold Reaction		Wassermann Reaction		Globulin in Cerebrospinal Fluid	Diagnosis
	Blood Serum	Cerebrospinal Fluid	Blood	Spinal Fluid	Cerebrospinal Fluid	
1	1221100000	4443331000	3+	4+	++	Cerebrospinal syphilis
2	5442110000	5555321000	4+	4+	++	Cerebrospinal syphilis
3	5555321000	5555321000	4+	4+	+	Cerebrospinal syphilis
4	4553210000	4553200000	4+	Neg	+	Cerebrospinal syphilis
5	2321000000	5555321000	4+	4+		Cerebrospinal syphilis
6	1330000000	2223331110	4+	4+	++	Cerebrospinal syphilis
7	2221000000	5531000000	4+	Neg	Neg	Cerebrospinal syphilis
8	1210000000	5554321000	4+	4+		Cerebrospinal syphilis
9	5555310000	5555432100	4+	4+	++	Cerebrospinal syphilis and cirrhosis of liver
10	2532110000	0011000000	4+	Neg		Syphilitic heart disease, large, hard smooth liver
11	1253110000	0000110000	3+	Neg	Neg	Syphilitic heart disease, large, hard liver
12	5521110000	1112000000	4+	4+		Syphilitic heart disease, large hard liver
13	5552100000	0012000000	3+	Neg	+	Secondary syphilis, history of toxic hepatitis
14	5532100000	0000100000	2+	Neg	Neg	Primary syphilis and arsenical hepatitis
15	1221000000	0000000000	4+	Neg	Neg	Primary syphilis
16	0220000000	0000000000	4+	Neg	Neg	Primary syphilis
17	2210000000	0010000000	3+			Primary syphilis
18	0232110000	0000110000	4+			Primary syphilis
19	0122100000	4441113321	Neg	Neg	+++	Meningococcal meningitis
20	0122100000	0000210000	Neg	Neg	Neg	Biliary tract neoplasm, liver normal (autopsy)
21	2221000000	0011000000	Neg	Neg		Parkinsonism
22	0110000000	0001210000	Neg	Neg	+	Miliary tuberculosis liver normal (autopsy)
23	1232100000	0011000000	Neg	Neg	+	Epidural abscess, liver normal (autopsy)
24	0454321000	0010000000	Neg	Neg		Primary tumor of liver (autopsy)
25	5544531000	0012100000	Neg	Neg		Portal cirrhosis of liver

in 4 of the 5 cases. The albumin was reduced in 3 of the 7 cases, but the average value was normal—4.13 Gm. In the 6 cases in which the plasma cholesterol and cholesterol esters were determined, the former was normal in 4 and low in 2 while the latter were normal in 3 and low in 3.

Comparison of the Colloidal Gold Reaction in the Blood Serum and in the Cerebrospinal Fluid—The colloidal gold reaction of the spinal fluid and that of the blood serum from the same patient may be the same or may differ greatly, depending on the disease process (table 7). The colloidal gold reaction was positive in the blood serum and negative in the spinal fluid of 7 patients with liver disease. This

group included 3 patients with syphilitic heart disease and large, hard livers (table 7, cases 10, 11, 12), 1 patient with portal cirrhosis (case 25), 2 with arsenical hepatitis (cases 13 and 14) and 1 with a hepatic tumor (case 24). In 4 cases of cerebrospinal syphilis, colloidal gold reactions were positive in the spinal fluid and negative in the blood serum, with increased globulin in the spinal fluid in 1 instance (cases 1, 5, 7, 8). On the other hand, in 3 similar cases the colloidal gold reactions in both the spinal fluid and the blood serum were positive, with increased globulin in the spinal fluid in 3 instances (table 7, cases 2, 3, 4). In 1 case (case 9), in which both syphilis of the central nervous system and hepatic cirrhosis were present, both the spinal fluid and the blood serum gave positive reactions. In 3 cases of early syphilis with no evidence of hepatic disease (cases 16, 17, 18) and in 3 cases of various conditions other than hepatic disease or syphilis (cases 21, 22, 23) there were negative colloidal gold reactions in both the spinal fluid and the blood serum. The spinal fluid globulin was increased in 2 of these cases. In 1 case (case 19) of meningococcic meningitis, with no clinically detectable hepatic disease, a positive colloidal gold reaction was obtained in the spinal fluid and a negative reaction in the blood serum.

COMMENT

In these studies there was a high incidence of positive colloidal gold reactions in the blood serums of patients with hepatic disease. The reactions were positive in 89 of the 96 cases of hepatic disease studied (92.7 per cent). Positive reactions were obtained in every case of cirrhosis of the liver, in all but a single case of acute parenchymatous disease of the liver and in all the cases of miscellaneous hepatic disease studied. The reaction was negative in a case of mild catarrhal jaundice with subsiding symptoms and in 6 cases of neoplastic disease of the liver, in 4 of which autopsy revealed minimal involvement or a few small malignant nodules.

The sensitivity of the colloidal gold reaction was of considerable clinical importance in several cases of hepatic disease, confirmed by autopsy or biopsy in 4 instances, in which bilirubin excretion, bromsulphalein retention and other tests were negative. In 1 of these cases (L. F. [table 1, case 31, a 47 year old woman with splenomegaly, macrocytic hyperchromic anemia, jaundice, reticulocytosis and normal blood fragility]), the colloidal gold reaction in the serum was repeatedly positive. Various tests, including the bromsulphalein retention, bilirubin excretion, hippuric acid, galactose tolerance, levulose tolerance and Takata-Ara tests, gave normal results. A small, firm, diffusely nodular cirrhotic liver was found at operation. Similarly, normal results were

obtained with one or more of the foregoing tests made in 3 cases of hepatic disease in which the diagnoses of portal cirrhosis, primary tumor of the liver and miliary infectious granuloma of the liver were confirmed at autopsy (table 1, case 4, table 3, case 12, table 4, case 10). The colloidal gold reaction, however, was persistently positive in all 3 cases. It is interesting to note that the bromsulphalein retention test in the 12 cases of hepatic disease in which it was used was positive in 6 cases and negative in 6, while the colloidal gold reaction was positive in 11 of the 12 cases.

While these studies were being completed Bauer¹⁷ reported somewhat similar observations on the colloidal gold reaction and compared his results with the Takata-Ara test. In my studies I found the Takata-Ara test less sensitive than the colloidal gold test. It was positive in 28 of 35 cases of hepatic cirrhosis, in 3 of 8 cases of acute parenchymatous liver disease, in 2 of 12 cases of neoplastic hepatic involvement and in 1 of 3 cases of miscellaneous hepatic disease, a total of 34 positive tests in 58 cases (58.6 per cent).

In cases of extrahepatic jaundice of short duration (such as that resulting from a stone in the common duct) in which the liver was found to be normal at operation, the colloidal gold reactions were negative regardless of the degree of jaundice (table 5, cases 1, 2, 3, 5, 6, 7). The amount of serum bilirubin present did not appear to alter the reaction. In cases of extrahepatic jaundice of long duration, however, with secondary liver involvement found at operation, the colloidal gold reaction was positive (table 4, case 1).

The reaction was negative in other diseases in which there was no clinically detectable pathologic change in the liver, as in acute and chronic nephritis, infectious diseases, neoplastic diseases and blood dyscrasias. The diagnosis of a normal liver was confirmed by autopsy, biopsy or laparotomy in 22 cases. In a case of lobar pneumonia (table 2, case 9) jaundice developed, the colloidal gold reaction was positive until the symptoms of hepatitis had subsided. Positive reactions were obtained in a case of subacute bacterial endocarditis and in one of passive congestion of the liver.

Observations of the colloidal gold reaction in syphilis indicate a high percentage of disease of the liver following antisyphilitic therapy (table 6). Five of the 8 positive colloidal gold reactions were in cases with histories of previous arsenical therapy, in 1 of these there had been hepatitis (table 6, case 7). However, 7 of the 12 negative reactions were found in cases with histories of similar arsenical therapy. Whether the positive reactions obtained in syphilitic serums represent subthreshold

17 Bauer, R. Eine neue Seroreaktion—Serum Goldsolreaktion, *Klin Wchnschr* 16 1570, 1937.

hepatic disease following arsenical therapy¹⁸ or whether they represent false positive reactions, related in some way to the altered globulin content apparently present in syphilis,¹⁹ cannot be concluded at this time.

The differences between the colloidal gold reaction of the blood serum and that of the spinal fluid in various diseases may be explained by the blood-brain barrier's acting as a semipermeable membrane which excludes such proteins as euglobulin and fibrinogen from the spinal fluid.²⁰ This permeability is altered in various pathologic conditions of the meninges, such as cerebrospinal syphilis and meningococcic meningitis.²¹

The studies of the plasma cholesterol esters are interesting in that they demonstrate the rather high incidence (66.2 per cent) of abnormal values in hepatic disease.²² Decreases in the cholesterol esters were

18 (a) O'Leary, P. A., Snell, A. M., and Bannick, E. G. Portal Cirrhosis Associated with Chronic Inorganic Arsenical Poisoning. Report of Two Cases, *J. A. M. A.* **90** 1856 (June 9) 1928. (b) O'Leary, P. A. Observations on the Treatment of Syphilis of the Liver, *ibid.* **96** 183 (Jan. 17) 1931. (c) Baldrige, C. W. The Relationship Between Antisyphilitic Treatment and Toxic Cirrhosis, *Am. J. M. Sc.* **188** 685, 1934. (d) Biskind, G. R., Epstein, N. N., and Kerr, W. J. Hepatic Complications in the Treatment of Syphilis, *Ann. Int. Med.* **7** 966, 1934. (e) Kellogg, F., Epstein, N. N., and Kerr, W. J. Hepatic Complications in the Treatment of Syphilis, *ibid.* **9** 1561, 1936. (f) Sager, R. V. Factors Responsible for Jaundice in Syphilis, with Special Reference to the Role of the Arsphenamines, *Arch. Int. Med.* **57** 666 (April) 1936.

19 (a) Noguchi, H. The Relation of Protein, Lipoids and Salts to the Wassermann Reaction, *J. Exper. Med.* **11** 84, 1909. (b) Winternitz, R. Ein Beitrag zur chemischen Untersuchung des Blutes rezent luetischer Menschen, *Arch. f. Dermat. u. Syph.* **93** 65, 1908. (c) Muller, R., and Hough, W. H. Vergleichende Globulinmessungen an luetischen Seris, *Wien. klin. Wchnschr.* **24** 167, 1911. (d) Takuda, K. Refractometric Studies in Human Syphilis with Special Reference to Changes During Treatment with Arsphenamine and Neoarsphenamine, *Arch. Dermat. & Syph.* **4** 512 (Oct.) 1921. (e) Bircher, M. A., and McFarland, A. R. The Globulin Content of the Blood Serum in Syphilis, *ibid.* **5** 215 (Feb.) 1922. (f) Lloyd, R. B. Protein Graphs in Syphilis with Their Relation to the Wassermann Reaction, *Indian J. M. Research* **19** 1055, 1932.

20 Greenfield, J. G., and Carmichael, E. A. The Cerebrospinal Fluid in Clinical Diagnosis, New York, The Macmillan Company, 1925.

21 (a) Greenfield, J. G. Some Modern Problems Connected with the Cerebrospinal Fluid, *Edinburgh M. J.* **43** 573, 1936. (b) Katzenelbogen, S. The Cerebrospinal Fluid and Its Relation to the Blood, Baltimore, Johns Hopkins Press, 1935.

22 (a) Thannhauser, S. J., and Schaber, H. Ueber die Beziehungen des Gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion, *Klin. Wchnschr.* **5** 252, 1926. (b) Adler, A., and Lemmel, H. Zur feineren Diagnostik der Leberkrankheiten. I. Cholesterin und Cholesterinester im Blute Leberkranker, *Arch. f. klin. Med.* **158** 173, 1928. (c) Epstein, E. Z.

observed in 47 of 71 cases of hepatic disease, in contrast, in the extrahepatic diseases the esters were decreased in 9 of the 30 cases. The incidence of low cholesterol esters in the various types of hepatic disease was approximately the same: 22 of 36 cases of cirrhosis (61.1 per cent), 9 of 12 cases of acute parenchymatous disease (75 per cent), 11 of 16 cases of neoplastic disease (68.8 per cent) and 5 of 7 cases of miscellaneous hepatic diseases (71.4 per cent). Extensive parenchymal damage was frequently associated with low cholesterol ester values (table 1, cases 27, 43, table 2, case 14, table 3, case 7). Changes in the cholesterol-cholesterol ester ratio paralleled the alteration of the plasma proteins except in the acute parenchymatous diseases, in which decreases in cholesterol esters were found more frequently than altered plasma protein values. The total plasma cholesterol values were not altered so readily, however, they were normal in 38, high in 18 and low in 21 of the 77 cases of hepatic disease studied. Normal values were observed in about half the cases of hepatic disease and in two thirds of the cases of extrahepatic diseases. An increase in plasma cholesterol was found in 4 of the 6 cases of extrahepatic jaundice, in contrast to the predominantly normal values observed in intrahepatic jaundice.

The poor prognosis associated with low cholesterol ester values²³ is demonstrated in 6 of the 7 cases in which the cholesterol esters were too low to determine. Death occurred in 6 cases within two months, 1 patient (table 2, case 7), with catarrhal jaundice, survived. In general, the decrease in cholesterol esters paralleled the severity of the hepatic injury, the cholesterol esters were frequently normal in the early stages of mild hepatic disease.

Variations in the plasma proteins were encountered frequently in 75 cases of hepatic disease in which protein values were determined. The globulin was increased in 43 cases and the albumin decreased in 45. The increase in globulin usually compensated for the decrease in albumin, so that the total plasma proteins were normal in all but 15 cases. It is interesting to observe that the lowest ratios—that is, the greatest increases in globulin and decreases in albumin—were associated with advanced hepatic destruction (table 1, case 14, table 2, case 14, table 3, case 7). The most marked variations in albumin and globulin values were found in cirrhosis of the liver, and the least marked variations were noted in the acute parenchymatous diseases.

The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, *Arch Int Med* **47** 82 (Jan.) 1931, Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases, *ibid* **50** 203 (Aug.) 1932.

²³ Adler and Emmel^{22b} Epstein^{22c}

The changes in concentration of the plasma proteins were related more closely to the severity and duration of the disease of the liver than to the state of nutrition or to loss of protein in the ascitic fluid. Moderately advanced hepatic disease without demonstrable ascites (table 3, cases 7, 23, 24, table 1, cases 1, 17, 21, 24) may produce greater variation in protein concentrations than less advanced hepatic disease with ascites (table 1, cases 8, 16, 36). One patient with a large, hard, irregular liver, cardiac decompensation and ascites of long duration had normal plasma proteins (table 1, case 41). No definite correlation could be found between malnutrition or inadequate protein intake and altered plasma proteins. Myers and Keefe,^{13f} Foley and associates^{18g} and Snell and Magath²⁴ have shown that the shifts in plasma proteins so frequently observed in hepatic disease are caused primarily not by deficient intake of protein or mechanical loss in the ascitic fluid but by defective formation of proteins. Holman, Mahoney and Whipple,²⁵ Kerr, Hurwitz and Whipple,²⁶ Sawada²⁷ and others²⁸ have concluded that the liver plays an important role in maintaining normal serum proteins.

The positive colloidal gold reaction does not depend primarily on a quantitative increase in globulin, a decrease in albumin or an inversion of the albumin-globulin ratio. Positive reactions were present in 29 of the 32 cases with normal plasma globulin values and in 21 of the 23 cases with normal albumin-globulin ratios. Conversely, in the control series the colloidal gold reaction was negative in 13 of the 15 cases with elevated plasma globulin values and in each of the 15 cases with low or inverted albumin-globulin ratios. The positive colloidal gold reaction may depend, therefore, on a qualitative rather than on a quantitative alteration in the plasma proteins. The work of Gros,^{14a} Kendall^{14b} and de Vries^{14c} indicates that the increased globulin found

24 Snell, A. M., and Magath, T. B. The Use and Interpretation of Tests for Liver Function. A Clinical Review, *J. A. M. A.* **110** 167 (Jan 15) 1938.

25 Holman, R. L., Mahoney, E. B., and Whipple, G. H. Blood Plasma Protein Given by Vein Utilized in Body Metabolism. II. A Dynamic Equilibrium Between Plasma and Tissue Proteins, *J. Exper. Med.* **59** 269, 1934.

26 Kerr, W. J., Hurwitz, S. H., and Whipple, G. H. Regeneration of Blood Serum Protein. III. Liver Injury Alone, Liver Injury and Plasma Depletion, the Eck Fistula Combined with Plasma Depletion, *Am. J. Physiol.* **47** 379, 1918.

27 Sawada, T. Biochemical Investigation of the Blood in Cases of Experimental Disturbance of Liver Function, *Jap. J. Gastroenterol.* **3** 38, 1931.

28 (a) Mann, F. C., and Magath, T. B. Die Wirkungen der totalen Leberexstirpation, *Ergebn. d. Physiol.* **23** 212, 1924. (b) Salvesen, H. A. Variations in the Plasma Protein in Non-Renal Conditions, *Acta med. Scandinav.* **72** 113, 1929. (c) Henriques, V., and Klausen, U. Untersuchungen über den Serumalbumin und Serumglobulingehalt des Serums unter wechselnden Umständen, *Biochem. Ztschr.* **254** 414, 1932.

in hepatic disease differs from that found in other diseases in that the euglobulin constitutes a higher percentage of the increase in globulin. It is suggested that since euglobulin is believed to play an important role in the colloidal gold precipitation¹⁵ and is thought to be specifically increased in hepatic disease, it may be responsible for the positive reactions obtained. Further work on the globulin fractions is being done.

SUMMARY AND CONCLUSIONS

The colloidal gold reaction of the blood serum was studied in a series of 96 cases of hepatic disease, grouped as follows: 46 cases of cirrhosis, 14 cases of acute parenchymatous disease, 25 cases of neoplastic involvement and 11 cases of miscellaneous hepatic disease. The diagnoses were confirmed by autopsy, biopsy or laparotomy in 34 cases: 11 in the first group, 2 in the second, 13 in the third and 8 in the fourth. The reaction was positive in each of 46 cases of cirrhosis, in 13 of 14 cases of acute parenchymatous involvement, in 19 of 25 cases of neoplasm and in each of 11 cases of miscellaneous hepatic disease. In the entire series, the reaction was positive in 89 of the 96 cases, or 92.7 per cent.

In several instances the colloidal gold reaction detected liver disease, later confirmed by operation or autopsy, which had not been detected by the usual clinical and chemical tests.

The colloidal gold reaction was negative with serums from 20 normal adults and in 73 of 75 cases of various extrahepatic diseases; normal livers were found in 22 of these cases at autopsy, biopsy or laparotomy.

Positive reactions were obtained in 8 of 20 cases of syphilis, in 1 of these 8 cases there was a history of hepatitis but in the others there was no demonstrable hepatic disease. The possibility of latent damage to the liver following arsenical therapy and the question of false positive reactions in syphilis are discussed. It is pointed out that the colloidal gold reaction of the spinal fluid and that of the blood serum may be the same or may differ greatly, depending on the effects of disease processes on the permeability of the blood-brain barrier.

The Takata-A1a reaction was positive in only 34 of 58 cases of hepatic disease (58.6 per cent), it was thus considerably less sensitive than the colloidal gold reaction.

The total plasma cholesterol was normal in 38 of the 77 cases of hepatic disease studied.

However, decreased values for plasma cholesterol esters were frequently associated with extensive parenchymal damage and were present in 47 of 71 cases of hepatic disease (66.2 per cent). The decrease paralleled the severity of the hepatic injury and was of prognostic significance, 6 of the patients whose cholesterol esters were too low to determine died within two months.

Changes in the cholesterol-cholesterol ester ratio paralleled the shifts in the plasma proteins in all types of liver disease except the acute parenchymatous diseases, in which lowered cholesterol esters were more frequent than altered plasma protein values

Variations in the plasma proteins were frequent in hepatic disease, globulin was increased in 43 cases, and albumin was decreased in 45 of the 75 cases studied. The increase in globulin was usually greater than the decrease in albumin, so that the total proteins were normal in 60 of the 75 cases.

The most marked albumin-globulin shifts occurred in cirrhosis of the liver and were associated with advanced hepatic destruction, the least marked variations were found in the acute parenchymatous hepatic diseases. The changes in concentration of the plasma proteins were related more closely to the severity and duration of the hepatic disease than to the state of nutrition or to the loss of protein associated with ascites.

The colloidal gold reaction does not depend primarily on a quantitative increase of globulin or on a low or inverted albumin-globulin ratio. Positive reactions were obtained in 29 cases of hepatic disease with normal plasma globulin values and in 21 cases with normal albumin-globulin ratios. The mechanism of the reaction is unknown. It is suggested that it may depend on a qualitative rather than on a quantitative variation in the plasma globulin and that the euglobulin may be an important factor in the reaction.

Drs. George F. Dick and Walter L. Palmer gave many suggestions during this study, and Miss Kathryn Knowlton and Miss Lois Seago gave technical assistance.

THE BRAIN IN MALIGNANT HYPERTENSION^{*}

A CLINICOPATHOLOGIC STUDY

EDWARD F ROSENBERG, M D

Fellow in Medicine, the Mayo Foundation

ROCHESTER, MINN

As a result of the original concepts of Volhard and Fahr,¹ a malignant (*bosartig*) form of hypertension was separated from the general group in 1914. In 1924, however, Wagener and Keith² described a syndrome of malignant hypertension and showed that this condition deserves the distinction of an entity, differing from chronic glomerulitis and benign hypertension on the basis of age incidence, a characteristic retinal picture, absence of anemia and frequent persistence of adequate renal function. This clinical concept of Wagener and Keith was further developed in investigations at the Mayo Clinic, the results of which were published in 1927,³ 1928,⁴ 1929,⁵ and 1931,⁶ and various pathologic studies of this disease have been reported from this institution by Can,⁷ Morlock⁸ and Odel.⁹ None of these works included any compre-

From the Division of Medicine, Section of Pathologic Anatomy and Section of Ophthalmology, the Mayo Clinic

^{*} Objection has been raised to the use of the term malignant hypertension. In this paper, the term has been used interchangeably with diffuse arteriolar disease with hypertension, group 4.

1 Volhard, F, and Fahr, K. T. Die Brightsche Nierenkrankheit. Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

2 Wagener, H. P., and Keith, N. M. Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch Int Med **34** 374-387 (Sept) 1924.

3 Keith, N. M. Classification of Hypertension and Clinical Differentiation of the Malignant Type, Am Heart J **2** 597-608 (Aug) 1927.

4 Keith, N. M., Wagener, H. P., and Kernohan, J. W. The Syndrome of Malignant Hypertension, Arch Int Med **41** 141-188 (Feb) 1928.

5 Kernohan, J. W., Anderson, E. W., and Keith, N. M. The Arterioles in Cases of Hypertension, Arch Int Med **44** 395-423 (Sept) 1929.

6 Keith, N. M., Barker, N. W., and Kernohan, J. W. Histologic Studies of the Arterioles in Various Types of Hypertension, Tr A Am Physicians **46** 66-70, 1931.

7 Can, E. F. Malignant Hypertension. The Histologic Changes in the Kidneys, Arch Int Med **53** 832-850 (June) 1934.

8 Morlock, C. G. Arterioles of the Pancreas, Liver, Gastrointestinal Tract, and Spleen in Hypertension, Arch Int Med **63** 100-118 (Jan) 1939.

(Footnote continued on next page)

hensive data regarding the brain. The purpose of the present study has been to survey the brain in cases of malignant hypertension, to catalogue the lesions present and, if possible, to correlate these lesions with symptoms that occurred in life.

When this study was in progress, the autopsy material at the Mayo Clinic included 17 brains of persons who had died of malignant hypertension. A review of the clinical data on the patients and the pathologic observations on the brains forms the basis of the present communication.

In the group of cases on which this study is based there were 5 women and 12 men, and this sex distribution agrees with the generally observed higher incidence of malignant hypertension among men. The diagnosis of malignant hypertension was based on the criteria of Keith, Wagener and Kernohan.⁴ The age range for the group was from 7 to 65 years, the mean age being 43.

The duration of life after the onset of symptoms varied from four to eighteen months and averaged eight and nine-tenths months, thus again justifying the designation of this disease as "malignant." The symptoms in this group were predominantly referable to the central nervous system. This predominance was perhaps somewhat more marked than would be noted in a more general review of malignant hypertension, the difference may be explainable by the fact that special efforts are made to secure permission for examination of the brain when outstanding evidences of cerebral damage have been present during life. However, it should be stated that practically all patients with malignant hypertension have some clinical evidences of cerebral disturbances.

OBJECTIVE FINDINGS

The objective findings in patients with malignant hypertension have been thoroughly described by the authors whom I have already mentioned, and I need only review briefly the findings in this series of patients.

In all of these patients high blood pressure was present, and at times the systolic pressure exceeded 200 mm. of mercury, in some of them it exceeded 250 mm. The diastolic pressure often exceeded 120 mm. Figure 1 illustrates a characteristic course with regard to blood pressure in these patients. A distinctive retinal picture was always present during life, this was characterized by narrowing and sometimes by sclerosis of the retinal arteries, flame-shaped hemorrhages, cotton wool exudates and edema of the optic disks. Evidence of cardiac damage

9 Odel, H. M. A Study of the Changes in the Arterioles of the Myocardium in a Group of Cases of Diffuse Arteriolar Disease with Hypertension, Group IV, Thesis, Minnesota University Graduate School, 1937, Arteriolar Changes in the Myocardium in Diffuse Arteriolar Disease with Hypertension, Group IV, abstracted, Proc. Staff Meet., Mayo Clin. **14** 210-214 (April 5) 1939.

was usually present, varying from simple enlargement of the heart, with accentuation of the aortic second sound, to advanced heart failure, with anasarca, orthopnea and cyanosis. Frequently when the patient was seen early renal function was good, and not uncommonly it was adequate even to the time of death. However, renal function often failed in the terminal stages.

Laboratory Data—The urine often showed albumin. Cylindruria was present in some instances, as were erythrocytes. A study of the chemistry of the blood was made, particularly with reference to renal function. These studies showed that severe renal insufficiency preceded death in 12 instances. It is well to stress, however, that 5 patients were without severe renal failure until death. Thus, patients in this group of cases of malignant hypertension always had so-called retinitis albuminurica with papilledema and may or may not have had renal insufficiency.

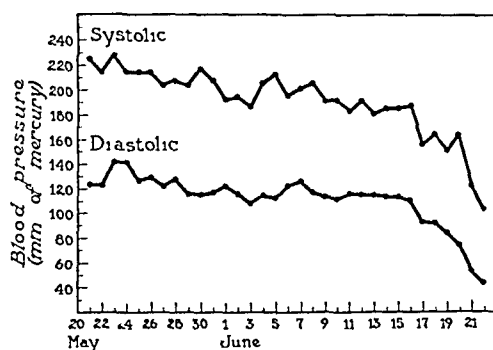


Fig 1 (case 14) —Blood pressure readings observed daily during final month of the terminal illness of the patient. Note how the high level of systolic and diastolic pressures was maintained until within a few days of death, despite gross clinical evidence of congestive heart failure during this period.

Anemia was present in 7 instances, but was severe in only 2.

Neurologic Examination—In the absence of a definite history of cerebrovascular accident with hemiplegia, the results of the neurologic examination were objectively negative in all but 2 instances, in these Babinski phenomena were present during life. These 2 cases will be referred to later.

Cerebrospinal Fluid—In 7 instances lumbar punctures were performed during life (table 1). It is interesting that in 5 of the 7 cases pressure of the subarachnoid fluid was elevated (28 to 35 cm of water) at the time of the first examination, whereas in 2 cases the pressure was normal (8 and 16 cm of water). Two patients who had elevated pressures on a single occasion had normal pressures on subsequent studies.

Thus, one cannot conclude that edema of the optic disks in a patient with malignant hypertension always denotes increased pressure of the

cerebrospinal fluid, although usually these two conditions are associated. Factors such as occlusion of the foramen occipitale magnum by the brain stem may prevent one's obtaining a true reading of the intracranial subarachnoid pressure by lumbar puncture.

The behavior of the cerebrospinal fluid in essential hypertension has been carefully studied in recent years. Admirable reports have been published by Shelburne, Blaine and O'Hare¹⁰ in the United States and

TABLE 1—*Correlation of Clinical Findings with the Presence of Edema of the Brain in Cases of Malignant Hypertension*

Case	Pressure of Cerebrospinal Fluid, Cm of Water	Choking of Disks, Diopters		Last Concentration of Urea, Mg per 100 Cc of Blood	Edema of Brain
		Right Side	Left Side		
1		3	1	34	Dura distended with fluid
2		Elevation	Elevation	134	Considerable excess of cerebrospinal fluid
3		1 to 2	1	158	No comment
4	30	4+	4+	54	No comment
5	32	4	4	657	Flattening of convolutions
6		2	2	108	Brain swollen
7		3	1+	24	No comment
8		2 to 3	2 to 3	492	Gyri widened and flattened, sulci narrow evidence of increased intracranial pressure
9		Edema, no definite elevation		144	Convolutions flattened, cortex slightly narrowed, owing to edema of brain
10		2	2	235	No comment
11	35	4 to 5	3 to 4	126	Convolutions flattened, grade 1+
12	16	1	1	116	No comment
13	30	1	2 to 3	42	No comment
14	8	Edema, no definite elevation		64	Brain edematous, grade 2+
15	28	7 to 8	7 to 8	86	Marked edema of brain
16		Edema, some elevation		101	Atrophy of convolutions, especially frontal, with increased amount of cerebrospinal fluid
17		2 to 3	2 to 3	116	Convolutions flattened, grade 1+ sulci narrowed

by Pickering¹¹ in England. The American authors stated that of 20 patients with severe hypertension in whom they observed an elevation of spinal fluid pressure, 19 had papilledema. Of 30 persons with hypertension in whom spinal fluid pressure was normal, only 2 had papilledema. Of 4 in whom blurring of the margins of the disks was present without definite elevation, all had normal pressures. Pickering reported

10 Shelburne, S. A., Blaine, D., and O'Hare, J. P. The Spinal Fluid in Hypertension, *J. Clin. Investigation* **11**: 489-496 (May) 1932.

11 Pickering, G. W. The Cerebrospinal Fluid Pressure in Arterial Hypertension, *Clin. Sc.* **1**: 397-413 (Dec) 1934.

that increased pressure in the subarachnoid fluid in patients with hypertension is an exceedingly grave prognostic finding. In the present series of cases the occurrence of increased pressure likewise proved of grave prognostic significance. Patients in whom Pickering observed a pressure of the cerebrospinal fluid exceeding 25 cm of water all died in from one day to ten months after the lumbar puncture. Of 13 such patients, 10 died of "uremia" and 3 of "convulsions." Both the American and the English workers have found, as I have, that not all patients who present the characteristic retinitis with papilledema and elevated spinal fluid pressure have evidence of renal insufficiency. Merritt and Fremont-Smith¹² stated that, except in rare instances, an elevated pressure of the cerebrospinal fluid occurs in hypertensive patients only if there is uremia, but in the present series of patients there were 2 (cases 4 and 13) who had elevated cerebrospinal pressure without uremia. At the meeting of the Société médicale des hôpitaux de Paris held on Jan 7, 1938, Riser, Planques and Becq,¹³ of Toulouse, reported that 4 patients with hypertension had died after lumbar punctures had been performed. Shelburne, Blaine and O'Hare¹⁰ stated that 1 of their group became psychotic shortly after a lumbar puncture. In the present series of cases, no accident has occurred after this procedure.

ARTERIOSCLEROSIS AND THE BRAIN IN HYPERTENSION

Sclerosis of the Larger Arteries—In the brain, as elsewhere in the body, sclerosis of the larger arteries appears to present a separate problem from that of the vascular effects of hypertension. The disease that is denoted clinically as arteriosclerosis of the central nervous system is associated pathologically with narrowed irregular tortuous basal arteries, beading and tortuosity of the smaller cortical arteries, thickening and opacity of the arachnoid and atrophy of the cortex with lipoidal degeneration of the neurons. In a group of patients with cerebral arteriosclerosis, Woltman¹⁴ found that 64.4 per cent had a mean blood pressure of 130 systolic and 78 diastolic. Certainly, then, arteriosclerotic changes cannot be considered as due primarily to the effects of hypertension. Indeed, Wartman¹⁵ could find gross arteriosclerotic changes in 80 per cent of brains in an unselected series of autopsies.

12 Merritt, H. H., and Fremont-Smith, F. *The Cerebrospinal Fluid*, Philadelphia, W. B. Saunders Company, 1937.

13 Accidents Following Lumbar Puncture in Cases of Hypertension, *Foreign Letters (Paris)*, J. A. M. A. **110** 1056 (March 26) 1938.

14 Woltman, H. W. Cerebrospinal Arteriosclerosis, *Minnesota Med* **5** 102-107 (Feb.) 1922.

15 Wartman, W. B. The Incidence and Severity of Arteriosclerosis in the Organs from Five Hundred Autopsies, *Am. J. M. Sc.* **186** 27-35 (July) 1933.

In the 17 patients of the present group the clinical grade of sclerosis of the peripheral arteries (a grading based on palpation of the brachial, radial, temporal and dorsalis pedis arteries) varied from "little" to grade 3 plus on a basis of 1 to 4 (table 2). It would seem from this that there is no constant relation of the severity of arteriosclerosis in the large peripheral arteries to the severity of hypertension. Hypertension was marked in all patients in this group, yet often there was only slight arteriosclerosis, thus, in 1 instance sclerosis was said to be slight, in 1 it was graded only 1 plus and in 4 it was graded 2. In several instances the data permitted comparison of the degree of

TABLE 2—*Grade of Arteriosclerosis in Cases of Malignant Hypertension*

Case	Grade of Arteriosclerosis *		
	Large Cerebral Arteries	Retinal Arteries	Peripheral Arteries
1	2 to 3	Present	2
2	3	Present	3
3	1	2	2
4	2	2 to 3	1+
5	0	2+	?
6	2	2 to 3	2
7	1	2 to 3	2 to 3
8	1	3	3
9	3	3	3+
10	2	Present	3
11	2	3+	?
12	2	1+ to 2	?
13	3	2+	3
14	1	1 to 2	2
15	0	0	Little
16	3	Considerable	3
17	2+	2+	2+ to 3

* On the basis of 1 to 4

sclerosis in the peripheral arteries with the degree of sclerosis observed by the ophthalmologist in the retinal arteries and arterioles. In most of these cases the disease was approximately of the same severity in the two sites (table 2). Thus, when a severe grade of sclerosis of the peripheral arteries is present in a patient with this disease, it would appear that the retinal vessels are usually similarly diseased. It is also of interest to compare the severity of the arteriosclerosis in the retinal and peripheral vessels with the degree of arteriosclerosis in the large vessels at the base of the brain. Severe changes in the retinal and peripheral arteries in these patients usually connoted a similar degree of change in the cerebral vessels (table 2). Thus, if one may judge from this small group, the presence of severe arteriosclerosis in the large peripheral and retinal arteries in a patient with malignant hyper-

tension usually indicates that a similar advanced degree of the arterial disease is present in the large cerebral vessels. Occasionally, however, this association is not striking (cases 7 and 8).

The Changes in Cerebral Arterioles—At various times during the past ten years there have been reports from this institution dealing with extensive surveys of the blood vessels in various organs as affected by hypertension. This series of researches now includes a general survey of the arterioles throughout the body in cases of malignant hypertension,⁴ a histologic study of the changes in the arterioles in specimens of pectoral muscle taken for biopsy in cases of hypertension,⁵ a clinico-pathologic study of the kidney and its vessels in cases of malignant hypertension, which appeared in 1934,⁷ a study of the vessels of the spleen, liver, pancreas and gastrointestinal tract,⁸ and a study of the heart.⁹

The changes that these workers have described in the arterioles of patients suffering from malignant hypertension are as follows: a slight increase in perivascular connective tissue, hypertrophy of the muscular coat of the media with an increase in the number of nuclear elements, a hyperplastic change affecting the internal elastic lamina, and proliferation of the endothelial and subendothelial cells, which sometimes is so extensive as to occlude the lumen almost completely. One of the outstanding achievements of these studies has been the establishment, by a reasonable biometric method, of data concerning the relative severity of arteriolar changes in persons suffering from hypertension of varying grades of severity. Furthermore, these studies have shown clearly that arterioles of different viscera are involved to differing degrees in the same patient. These workers have all used for measuring the vessels the plan outlined by Kernohan, Anderson and Keith.⁵ By this method the thickness of the arteriolar wall is measured in four places, and then an average of these four values is compared with the average diameter of the lumen, established by two measurements made at right angles to each other. The resulting ratio, when studied for a large number of vessels, gives some indication of the increased resistance that the flow of blood must encounter in the organ studied. The method has been adopted elsewhere by various workers,¹⁶ who have confirmed its usefulness.

Histologic studies were made of the 17 brains in this series, with special regard to the changes that had occurred in the measurements

16 (a) Pilcher, J. F., and Schwab, E. H. Arteriolar Changes in Essential Hypertension. A Preliminary Report, *Texas State J. Med.* **28** 665-668 (Feb.) 1933. (b) Murphy, F. D., and Grill, J. So-Called Malignant Hypertension. A Clinical and Morphologic Study, *Arch. Int. Med.* **46** 75-104 (July) 1930. (c) Moritz, A. R., and Oldt, M. R. Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am. J. Path.* **13** 679-728 (Sept.) 1937.

of the arterioles. Similar studies were also made of brains of 15 persons in whom there had been no evidence of hypertension during life or at autopsy. The disease causing the death of the control patients varied (table 3). Observations of the blood pressure had been made during life in all of the controls. The blood pressures never exceeded 140 mm of mercury systolic or 90 mm diastolic, and the weights of the heart at autopsy all fell within the range of normal, that is, they did not exceed 400 Gm for the men and 350 Gm for the women. The 15 control patients were chosen in such a manner that the age and sex corresponded to those of the group with hypertension (cases 16 and

TABLE 3—*Control Series*

Num ber	Age, Yr	Sex	Cause of Death	Weight of Heart, Gm	Mean Ratio of Wall to Lumen, Entire Brain
1	41	♀	Pneumonia	300	1.48
2	53	♀	Chronic pulmonary tuberculosis, pneumonia	235	1.33
3	47	♂	Cerebral contusions and lacerations	382	1.31
4	32	♂	Fractured skull with lacerations of brain	346	1.31
5	23	♂	Retrovertebral abscess	287	1.37
6	19	♂	Cerebral contusions and lacerations	345	1.35
7	57	♂	Carcinoma of ileum, peritonitis	285	1.32
8	28	♂	Knife wound of neck	336	1.33
9	50	♂	Cancer of larynx with obstruction	327	1.30
10	57	♂	Cancer of rectum, pneumonia	212	1.33
11	49	♀	Stricture of bile ducts, hepatic coma	312	1.34
12	59	♂	Cancer of stomach	242	1.36
13	58	♂	Cerebral contusions and lacerations	335	1.33
14	30	♀	Chronic ileus with obstruction	230	1.44
15	6	♀	Contusions and lacerations of brain	130	1.42
Mean ratio of wall to lumen					1.35

17 were added at the end of the work, and no cases were included as controls.)

The tissues studied were taken from material obtained at routine necropsy, fixed in 10 per cent solution of formaldehyde U S P, blocked in paraffin and stained. The differential stains used to study the vessels included the Van Gieson stain, the Mallory-Heidenhain and the Weigert elastic tissue stain.

As a result of the careful experiments of Moritz and Oldt,^{16c} it is now known that methods of preparation of tissues and the physiologic condition of the vessel wall at the time of death have no influence on the ratio of the wall to the lumen as determined by the methods used in my study.

The thickness of the walls and the diameters of the lumens were studied in ten vessels in each of six regions of the brain. These regions were in each instance the frontal cortex, the parietal cortex, the occi-

pital cortex, the hypothalamic area, the medulla and the meninges. Measurements were made according to the technic of Kernohan, Anderson and Keith.⁵ The average for ten vessels from each region was taken to be an indication of the nature of the vessels in that part of the brain. The outside diameter of the vessels studied fell approxi-

TABLE 4—*Mean Ratio of Wall of Arterioles to Lumen in Different Regions of Body*

Region	Ratio	
	Persons Who Did Not Have Hypertension	Persons Who Died of Malignant Hypertension
Pectoral muscle (Kernohan, Anderson and Keith)	1 2 0	1 1 1
Kidney (Cain)	1 1 82	1 0 7
Heart (Odel)	1 2 00	1 1 95
Abdomen (Morlock)		
Pancreas	1 2 45	1 1 24
Liver	1 2 31	1 1 14
Gastrointestinal tract	1 2 13	1 1 14
Spleen	1 1 32	1 1 04
Brain	1 3 5 *	1 1 7 †

* The ratio was computed from 900 vessels

† The ratio was computed from 1,020 vessels

TABLE 5—*Mean Ratio of Wall of Cerebral Arterioles to Lumen in Different Regions*

Region	Ratio	
	Persons Who Did Not Have Hypertension*	Persons Who Died of Malignant Hypertension†
Frontal cortex	1 3 3	1 1 5
Parietal cortex	1 3 3	1 1 5
Occipital cortex	1 3 2	1 1 2
Hypothalamic area	1 3 8	1 1 8
Medulla	1 3 8	1 1 8
Meninges	1 3 6	1 1 8

* Each ratio was computed from 150 vessels measured

† Each ratio was computed from 170 vessels measured

mately between 20 and 80 microns, thus, my results are comparable to those of the men who have preceded me in this work at this institution (tables 4 and 5 and figs 2 and 3). For the cerebral arterioles studied, it was found that the mean ratio of wall to lumen was 1 1 7 for the brains of persons that had died of malignant hypertension, whereas for the normal controls this mean ratio was 1 3 5 (table 4). Different

regions of the brain were noted to have only slightly differing values for these ratios, and these slight variations were noted both in the control group and in the persons who had died of hypertension (table 5)

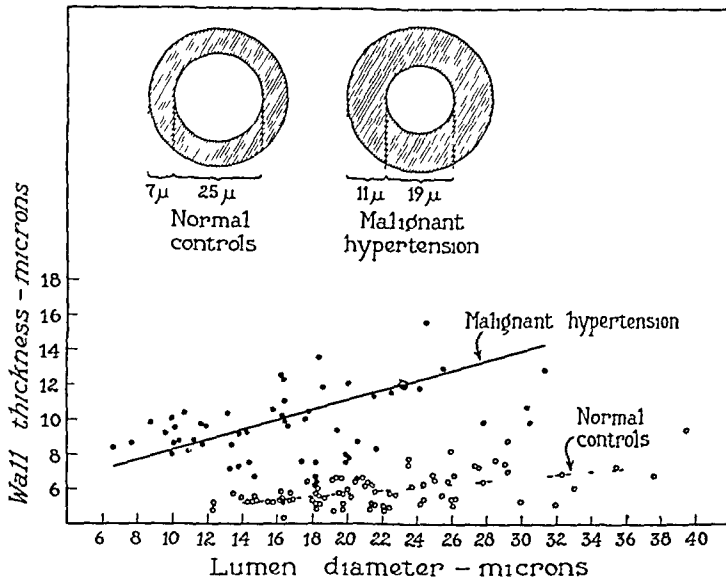


Fig 2—Comparison of the thickness of the wall and the diameter of the lumen of cerebral arterioles in cases of malignant hypertension and in the control series. The continuous lines represent the means for these measurements in each group. Arterioles in brains of persons suffering from hypertension have thicker walls than those of the controls, and for a wall of given size the lumen is narrower in the arterioles of persons suffering from hypertension than in those of the controls. Inserts, drawn to scale, illustrate diagrammatically the relative mean measurements for the cerebral arterioles in persons suffering from malignant hypertension and in the controls.

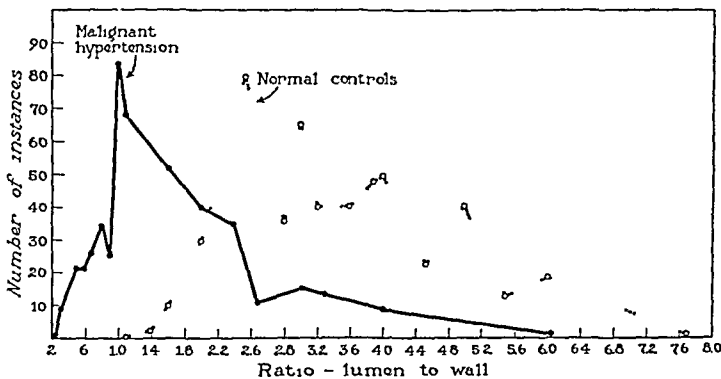


Fig 3—Frequency distribution of the ratios of the diameter of the lumen to the thickness of the arteriolar wall for the controls and for persons suffering from malignant hypertension. There is overlapping of the two curves, but the peaks are significantly separated.

Histologic Study of the Arterioles—A histologic study of the cerebral arterioles must take into account the changes in these vessels that result simply from aging. This subject recently was reviewed by

Baker,¹⁷ who concluded that the cerebral arterioles are distinguished from those elsewhere in the body by several features (1) The internal elastic lamina of the cerebral vessels is thicker than in vessels of similar size elsewhere, (2) collagen (hyalin) may make up the bulk of the wall of the cerebral arterioles, the muscle being irregular in occurrence or often entirely absent, (3) as the vessel diminishes in size its structure becomes simpler, so that what would be called fibrosis elsewhere is normal for the cerebral arteries. Baker found that with age (and independent of hypertension) there occur (1) thickening and reduplication with fraying of the internal elastic lamina and (2) progressive reduction in the muscular elements of the media with replacement by fibrous tissue. General thickening of the arteriolar wall with reduction of the caliber of the lumen was not noted by Baker as a feature of the changes in these vessels due to age.

On the other hand, thickening of the wall of arterioles was encountered in many sections that I examined from the brains of patients with hypertension, and this thickening was usually associated with reduction of the caliber of the lumen. In a general way, this thickening was due to an increase in the thickness of each of the three coats of the vessel (fig 4). Thus, in intimal lining, the muscular media and the fibrous adventitia took part in the changes observed. There was considerable variation in the extent to which these coats participated in the thickening. Intimal proliferation was seen frequently, but by no means in all the vessels encountered (fig 5). As a cause of general reduction of the width of the arteriolar stream bed of the brain, intimal proliferation appeared less important than the changes that occurred in the medial coat. Little degeneration was seen in the intimal or the medial coat. Vacuolar and hydropic degeneration was insignificant as a pathologic feature of these vessels, as were hyalinization and necrosis. The latter degenerative changes appeared to occur only as end stages in the disease process that affected the arterioles in malignant hypertension (fig 6).

The internal elastic lamina partook of the general hypertrophy affecting the vessel wall, and when examined in the specimens stained with an elastic tissue stain, this layer was usually seen to be comparatively thicker than in similarly sized vessels in control specimens. Not uncommonly this thick lamina was frayed or reduplicated, and with the elastic tissue stain strands of fibers could be seen to ramify throughout the other coats of the vessel (figs 5 and 7). This is the so-called elastosis. This ramification of elastic fibers also occurs occasionally in normal vessels, but the fibers are much less thick than in vessels from

17 Baker, A. B. Structure of the Small Cerebral Arteries and Their Changes with Age, *Am J Path* 13 453-461 (May) 1937.

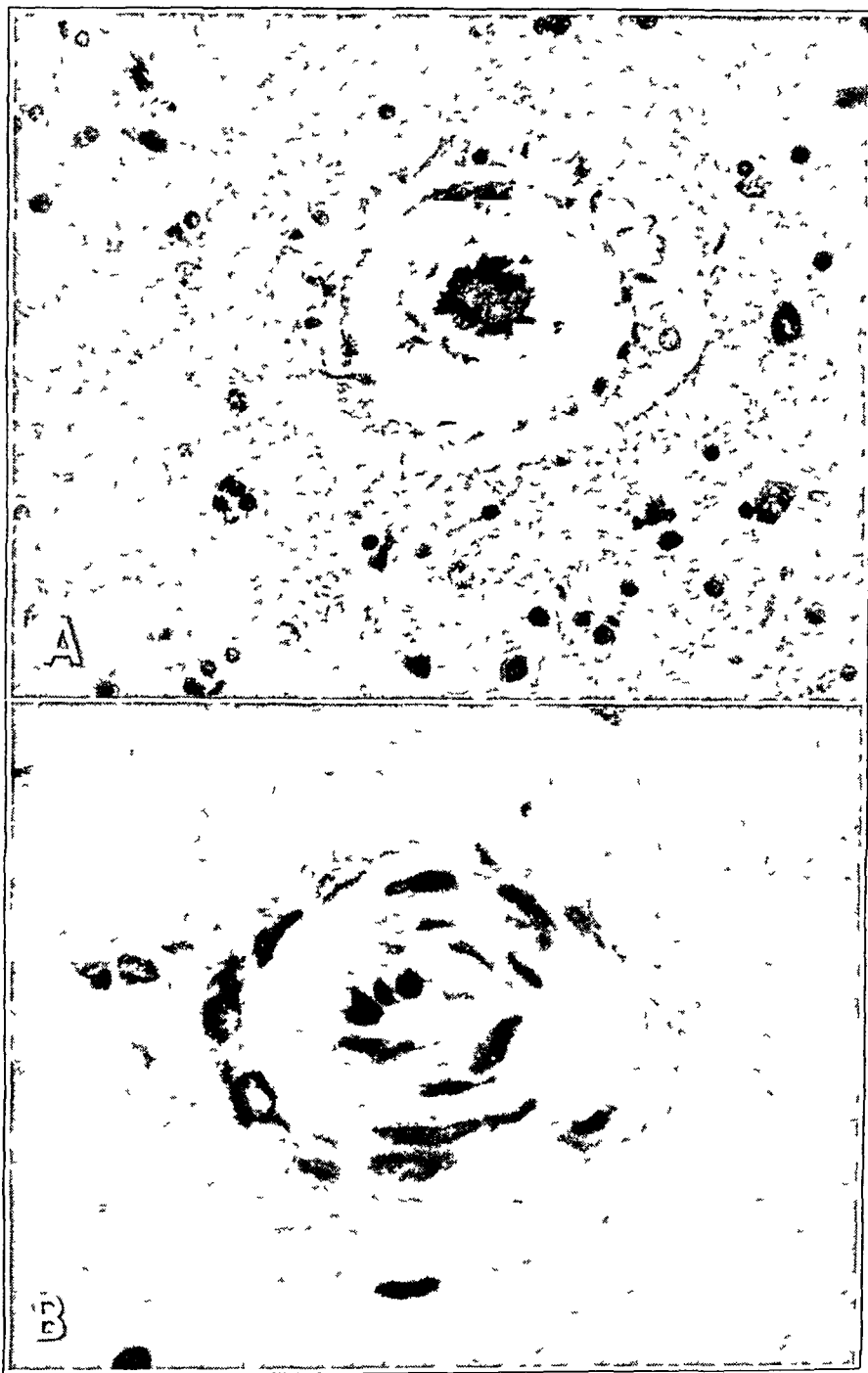


Fig 4—*A* (case 17), section from the occipital lobe ($\times 300$), showing markedly hypertrophied arteriolar wall with narrowed caliber of the lumen *B* (case 13), section from the left frontal lobe ($\times 480$), showing markedly hypertrophied arteriolar wall with narrowed caliber of the lumen Slight hyaline changes are evident in the wall Hematoxylin and eosin

the brains of patients with hypertension and consequently much more difficult to follow in the microscopic preparations. Fractures in the internal elastic lamina are not uncommon in the vessels of persons suffering from malignant hypertension.

In the medial coat of many arterioles in the brains of persons with hypertension, there could be seen an increase in the size of the individual cells and of their nuclei, and often there appeared to be

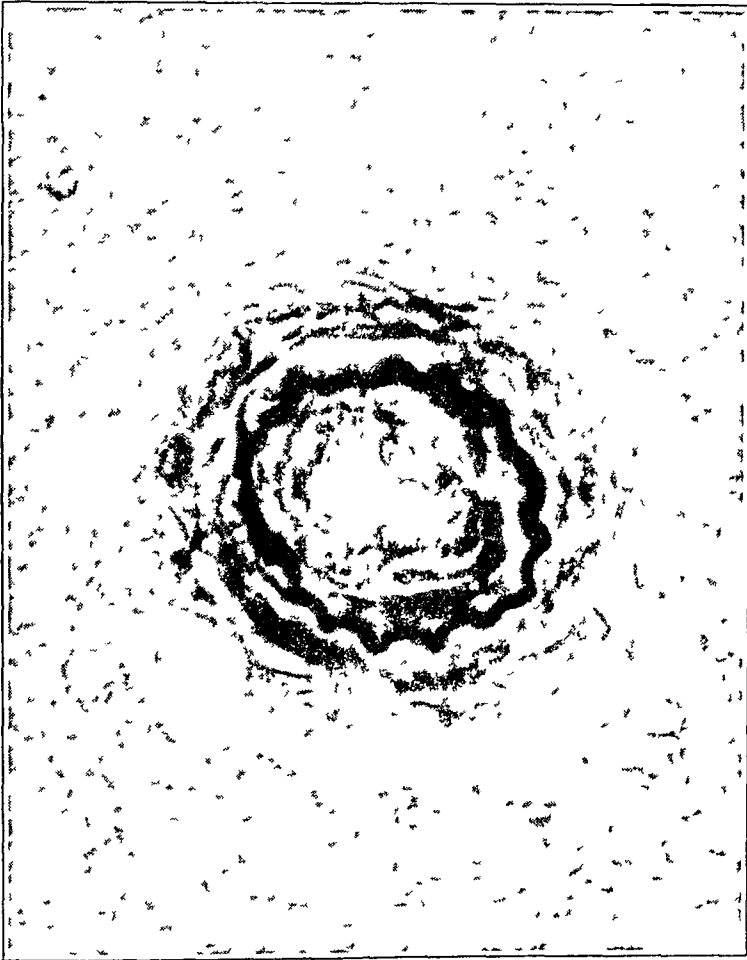


Fig 5 (case 12) —Arteriole in the region of the right parietal lobe, showing hypertrophy of arteriolar wall, thickened frayed internal elastic lamina and hyperplasia with thickening of the intimal coat. Weigert elastic tissue stain, $\times 700$.

such an increase in the number of cells that this portion of the wall was thick and hypertrophic. The adventitial fibrous coat was frequently thickened, and in the Van Gieson-stained sections it often appeared as a red band about the vessel. I have seen little infiltration of the medial or the intimal coat with fibrous tissue cells, although the adventitial fibrous coat was in general thick as compared with that of normal vessels. Not uncommonly one found a few lymphocytes in the thickened adventitial coat, and in a number of brains examined these peri-

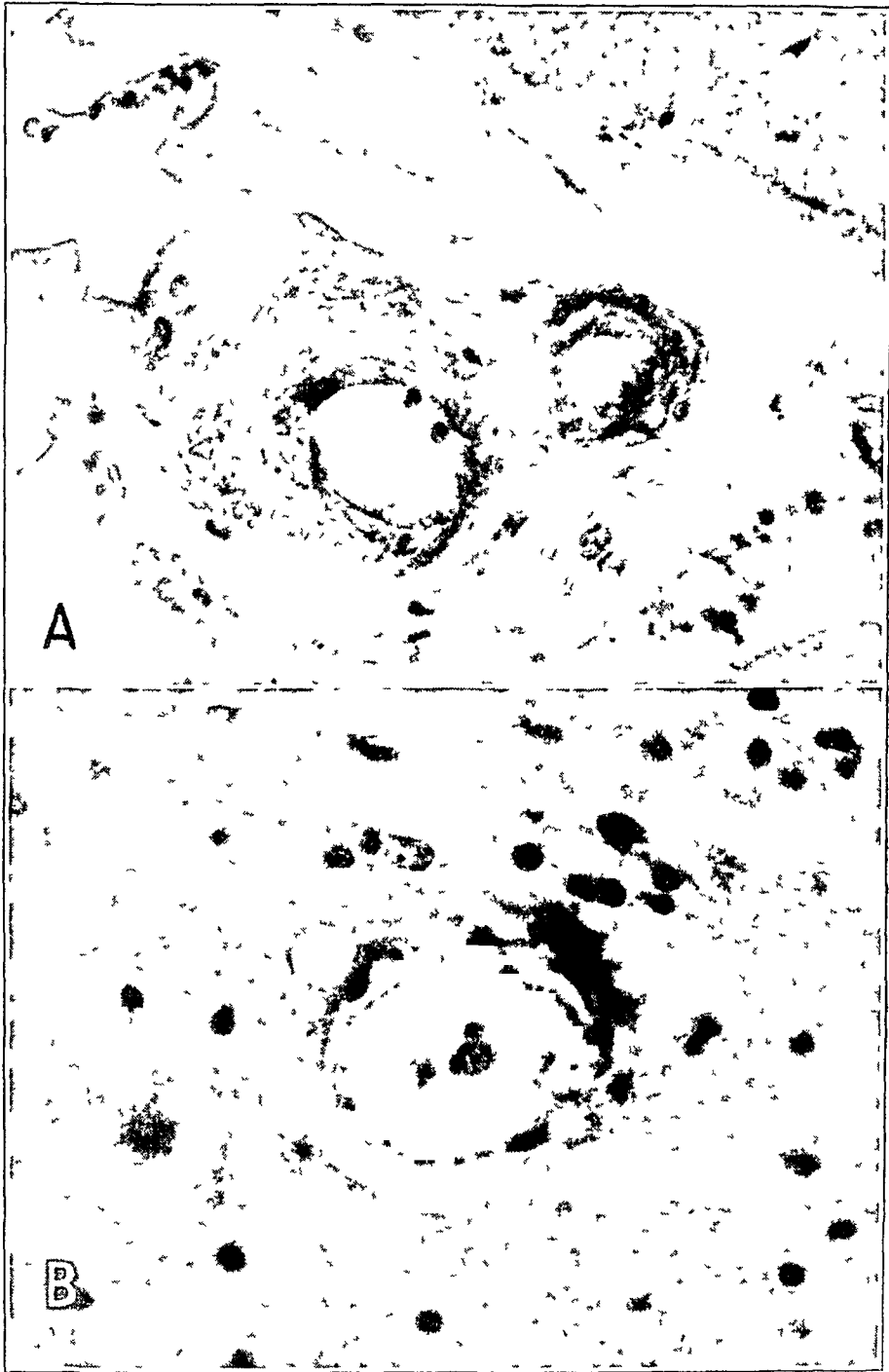


Fig 6—*A* (case 3), arterioles in the meninges, showing hypertrophy of the walls with vacuolar degeneration, $\times 400$ *B* (case 15), arteriole in the region of the parietal lobe, showing hypertrophy and marked necrosis, with hyaline degeneration of the wall, $\times 780$ Hematoxylin and eosin

vascular lymphocytes had increased in number to form a definite collar about the vessels, as described in the section on "inflammatory lesions." Calcification was rare in the cerebral arterioles, being seen only occasionally as a band of calcified droplets lying between the medial and the adventitial coat.

Accordingly, the study of the arterioles in the brain reveals that there is often present hypertrophy of arteriolar walls with reduction of the caliber of the lumen. It would appear that a definitely increased



Fig 7 (case 3)—Arteriole in the region of the left frontal lobe, showing hypertrophy and fraying of the arteriolar wall, with lamination and thickening of the internal elastic lamina. Weigert elastic tissue stain, $\times 700$.

anatomic barrier often exists in this disease, which may obstruct the flow of blood beyond the degree of resistance normally offered by this arteriolar portion of the vascular tree. For some unknown reason, not every tissue shares alike in the extent of change in the disease, but the brain is frequently severely affected. The heart usually escapes with slight changes.⁹ Essentially, the lesions in the brain observed in the patients who had suffered from malignant hypertension were similar to the changes that other investigators have found in persons with

benign hypertension. They differed only in their advanced degree and severe nature. Necrosis of arterioles, which has not infrequently been described as the *sine qua non* of malignant hypertension, was extremely rare in these specimens. In table 6 I have correlated the severity of the changes in the caliber of the cerebral arterioles with the occurrence of destructive cerebral lesions. It appears that no definite relationship exists between these data.

In 1926 Bordley and Baker¹⁸ published a study of the brain in cases of hypertension. They concluded that arteriosclerosis is more marked in the medulla than elsewhere in the brain in such cases and that it is possible to explain chronic hypertension on the basis of localized

TABLE 6—*Cerebral Vascular Lesions and Ratio of Wall of Cerebral Arterioles to Lumen in Cases of Malignant Hypertension* *

Case	Massive Hemorrhage	Large Infarct	Multiple Small Hemorrhages	Multiple Small Infarcts	Average Ratio of Wall to Lumen
1	+		+	+	1.18
2			+	+	1.202
3			+	+	1.15
4	+	+	+	+	1.16
5			+		1.28
6	+				1.13
7	+		+	+	1.21
8			+	+	1.25
9			+	+	1.19
10					1.13
11			+		1.14
12				+	1.12
13			+	+	1.14
14			+		1.12
15		+		+	1.13
16			+	+	1.20
17		+	+	+	1.16

* The presence of the lesion is indicated by +.

arteriosclerosis in the region of the vasomotor center. This arteriosclerosis, they concluded, probably results in local anemia, which, according to the experiments of Anrep and Starling,¹⁹ would give rise to systemic hypertension. This conception has been vigorously and adequately opposed by many workers (Ruhl, 1927,²⁰ Keith, Wagener and

18 Bordley, J., III, and Baker, B. M., Jr. A Consideration of Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension. A Preliminary Report, *Bull. Johns Hopkins Hosp.* **38**: 320-321 (April) 1926, Arteriosclerosis of the Cerebral Vessels and the Pathogenesis of Hypertension, *ibid.* **39**: 229-264 (Oct.) 1926.

19 Anrep, G. V., and Starling, E. H. Central and Reflex Regulation of the Circulation, *Proc. Roy. Soc., London*, s. B **97**: 463-487 (Feb. 2) 1925.

20 Ruhl, A. Wie weit ist der genuine arterielle Hochdruck anatomisch bedingt? *Deutsches Arch. f. klin. Med.* **156**: 129-161 (Aug.) 1927.

Kernohan,⁴ 1928, Cutler,²¹ 1928, and Tuthill, 1931²²) My measurements of the arterioles of the medulla in 17 patients with severe hypertension show considerable narrowing of the lumen. However, this does not appear to be more marked than for any other of the regions studied (table 5)

CEREBRAL LESIONS IN MALIGNANT HYPERTENSION

The brain is seriously damaged in malignant hypertension. Probably no vital organ save the kidney is more uniformly or more extensively involved by this disease. A review of the lesions that were observed in the brains in the present series will serve to illustrate this fact.

The two major pathologic processes that damage the brain in malignant hypertension are hemorrhage and infarction.

Hemorrhage—A large variety of sites and a considerable variation in form characterized the hemorrhages in these brains. Among the 17 brains studied, there were 4 with massive hemorrhage. The brain in case 6 is typical. A large cavity filled with blood, involving the corpus striatum and the internal capsule, was observed in the left hemisphere. The hemorrhage had ruptured into the ventricles. This was a death-dealing blow for the patient, who died within twelve hours after symptoms of it appeared. In each of these 4 instances the large hemorrhage had torn its way into the ventricles. In 3 of these the hemorrhage was cerebral and had ruptured into the lateral ventricles, and in 1 it was cerebellar and had ruptured into the fourth ventricle. Death always occurred promptly when the hemorrhage ruptured into the ventricular system. Severe renal insufficiency was present in 1 instance (case 6) and absent in 3 (cases 1, 4 and 7) when the large hemorrhage occurred.

A second variety of hemorrhage encountered was small and spotty, consisting of regions of hemorrhage measuring from 1 mm to 2 cm in diameter (fig 8). These were distributed irregularly throughout the white matter of the cerebrum and cerebellum in 5 instances (cases 2, 3, 8, 16 and 17). Microscopic examination showed some to be homogeneous regions of hemorrhage without obvious source and others to be so-called ring hemorrhages, or circular zones of hemorrhage about the small vessels. These small hemorrhages were associated in each case with numerous infarcts of about the same size and distribution as the hemorrhages. In all these 5 cases there was marked nitrogen retention at the time of death, the last recorded values for blood urea being 134, 158, 492, 101 and 116 mg per hundred cubic centimeters respectively.

21 Cutler, O. I. Relation of Arteriosclerosis of the Cerebral Vessels to Hypertension. Distribution of Arteries Supplying Pons and Medulla, *Arch. Path.* 5: 365-379 (March) 1928.

22 Tuthill, C. R. Hypertension in Relation to the Blood Vessels of the Medulla Oblongata, *Arch. Path.* 11: 760-765 (May) 1931.

In case 8 the number of hemorrhages was so great that it suggested to Dr Kernohan hemorrhagic encephalitis of the arsenical type, and chemical analysis showed the presence of 0.12 mg of arsenic per hundred grams of brain substance. In certain types of encephalitis, the presence of arsenic in excess of 0.1 mg per hundred grams is believed to be of etiologic significance. However, the relationship of the arsenic to the hypertension in this instance is not clear.

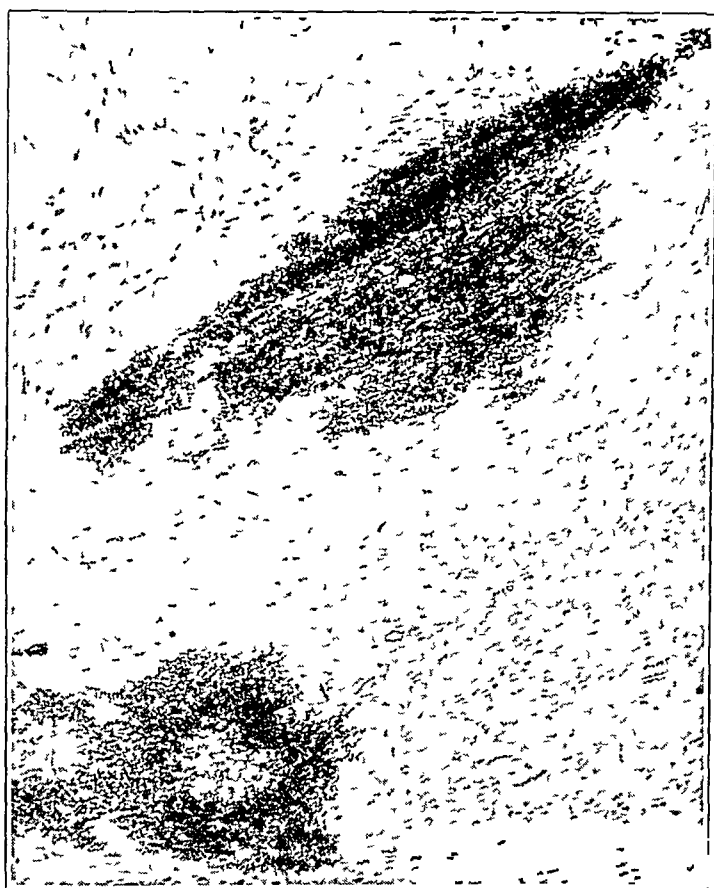


Fig 8 (case 8)—Small, "spotty" hemorrhage and "ring hemorrhage" in a section from the thalamus. Hematoxylin and eosin, $\times 60$.

Bleeding onto the surfaces of the brain occurred in cases 1, 14 and 17. In case 1 small hemorrhages were found beneath the arachnoid, scattered about the surface of the cerebral and cerebellar hemispheres and penetrating between the convolutions. In case 14 the hemorrhages were subdural. In case 17 there was a small region of subarachnoid hemorrhage over the superior surface of the right parietal lobe. Subependymal hemorrhage was found in the anterior horn of the lateral ventricle in case 7.

Capillary hemorrhages were observed frequently (fig 9). They were even more common than any of the three types of bleeding just

described and occurred in 8 instances (cases 2, 3, 4, 5, 9, 11, 13 and 14). Of these instances, severe renal insufficiency was present in 6 (cases 2, 3, 5, 9, 11 and 14) and absent in 2 (cases 4 and 13).

Of these various forms of hemorrhage, the massive and the spotty were definitely destructive of brain tissue and doubtless were responsible for symptoms during the life of the patient. The capillary hemorrhages may also have caused considerable irritation to the brain. Furthermore, the frequent association of the different types of hemorrhage with one



Fig 9 (case 2) —Minute capillary hemorrhages in a section from the region of the hypothalamus. Hematoxylin and eosin, $\times 55$.

another and with other types of lesions in the same brain probably means that in these instances considerable portions of the brain had been thrown out of function.

Infarctions —Infarcts in these brains are divided into two varieties: single large and multiple miliary infarcts.

Single large infarcts were observed in cases 4, 15 and 17. In case 4 the infarct doubtless dated from a cerebrovascular episode which, according to the history, had occurred six months before death. This infarct involved the basal ganglia on the left, measured 0.5 by 4 by 6

cm and was associated with a large recent hemorrhage on the right side which had ruptured into the ventricles. In the second instance (case 15) the large single infarction took place in a child aged 7 years and appeared grossly as widespread necrosis of the surface of the left side of the brain, involving the temporal, occipital and parietal lobes. Roughly, this necrotic region corresponded to the surface distribution of the middle cerebral artery. On section of the brain the infarct was shallow, involving only the gray matter and the adjoining white matter. Doubtless this infarct was superficial rather than deep because of some peculiarity of the collateral circulation in the brain of the child. In case 17, the infarct was similar to that observed in case 4. In these 3 cases there were small multiple infarcts in addition to the large infarct.

Multiple military infarcts, the second form, must be of outstanding importance in these cases because of the frequency with which it occurs and its wide distribution. These multiple military infarcts were found in 12 instances (table 7 and figs 10, 11 and 12). They were widespread, involving not only the basal ganglions but also the cortex, the white matter, the basal nuclei, the brain stem and the cerebellum. They varied in size from regions 5 or 6 mm in diameter to minute softenings seen only with the aid of the microscope. In 4 of these 12 cases no lesion could be seen on gross examination, but the softenings were found in microscopic sections. Thus, the brain cannot be assumed to be intact unless careful microscopic search for these lesions has been made. In the remaining 8 cases both gross and microscopic lesions were observed. It is important to realize that the extent of these infarcts and the amount of cerebral damage that they cause cannot be accurately estimated unless many sections are studied. I was often impressed with the fact that large quantities of brain substance had been destroyed by these infarcts, and the clinical pictures often suggested the same conclusion. Degenerated blood in the form of blood pigment was seen frequently in these infarcts and suggested that the insults had been occurring over long periods, probably in "crops," as Pal²³ suggested. Table 6 illustrates the frequency with which destructive lesions were encountered.

Spielmeyer²⁴ expressed the opinion that some of these infarcts are due to vasospasms. His opinion was based on the observation of circumscribed regions, necrotic and destroyed, without his being able to demonstrate any obstruction in the vessels. This has often been my own experience. However, some infarcts in this series of brains had

23 Pal, J. Ueber die zerebralen Insulte und den Angiospasmus der Hyper-toniker, *Wien klin Wchnschr* **44** 1297-1299 (Oct 16) 1931.

24 Spielmeyer, W. Vasomotorisch trophische Veranderungen bei zerebraler Arteriosklerose, *Monatschr f Psychiat u Neurol* **68** 605-620 (March) 1928.

adjoining thrombosed vessels (fig 16) Volhard and Fahr¹ cited this opinion of Spielmeyer as confirming their own hypothesis of the occurrence of "vasospastic insults" in the brain Hiller²⁵ cited two good rules for the acceptance of a lesion of the brain as angiospastic (1) There must be absence of true vascular obstruction in the presence of a lesion, or (2) there must have been absence of a lesion in the presence of loss of function He expressed the opinion that a pathologist may be able to say whether a lesion has been caused by a vascular disorder and may be able to describe the adjoining vessels but will not be able to state the type of functional vascular change that occurred during life The last word, he pointed out, will have to wait on studies of the cerebral circulation in the living subject

At this point are included for comparison figures cited in 1937 by Jaffé²⁶ regarding the destructive lesions in the brains of patients with essential hypertension He stated that in 20 per cent of patients with this disease death was directly due to encephalic injuries Of these 20 per cent, he found infarctions in the brains of 13 per cent and hemorrhage in the remaining 7 per cent It is of interest to compare these figures with the results of the study of the present group of patients with malignant hypertension Cerebral hemorrhage caused the death of 4 patients (24 per cent), and some type of destructive lesion was found in 12 (71 per cent) of the entire group of patients with malignant hypertension Thus the brain suffers destructive lesions with relatively great frequency in this more severe form of the disease

Inflammatory Lesions—There is considerable theoretic interest in the presence of inflammatory lesions in tissue from patients with severe hypertension The cause of this disease has at various times been attributed to bacteria, and a case of severe vasospastic hypertension was recently reported from the Mayo Clinic in which the patient recovered after removal of infected tonsils²⁷ Klemperer and Otani²⁸ and, recently, Rosenberg, Keith and Wagener²⁹ have reported instances of severe hypertension in which marked inflammatory reactions could be seen in many blood vessels

25 Hiller, F, in Bumke, O, and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol 11, pp 331-338

26 Jaffé, R H The Pathology of the Cardiovascular, Cerebral and Renal Changes in Essential Hypertension, Radiol Rev & Mississippi Valley M J **39** 7-12 (Jan) 1937

27 Haben, H C, and Wagener, H P Acute Vasospastic Hypertension, Minnesota Med **20** 180-182 (March) 1937

28 Klemperer, P, and Otani, S Malignant Nephrosclerosis (Fahr), Arch Path **11** 60-117 (Jan) 1931

29 Rosenberg, E F, Keith, N M, and Wagener, H P Diffuse Arterial Disease with Hypertension Two Unusual Cases of Contrasting Types, Arch Int Med **62** 461-481 (Sept) 1938

TABLE 7—Data on Persons Who Died of Malignant Hypertension

Case, Terminal Sex Urea, Mg and per 100 Cc Age of Blood	Cerebral Symptoms	Neuro- pathologic Observations	Postmortem Observations in Brain			Inflammatory Features	Comment
			Edema	Hemorrhages	Infarcts		
1 ♀ 45	Transient hemiplegia, tinnitus, impaired memory, vertex headaches, terminal hemiplegia with aphasia	None until onset of hemiplegia	Dura distended with fluid	Large hemorrhage of right cerebral hemisphere with rupture into ventricles, multiple small subarachnoid hemorrhages	Numerous microscopic infarcts	None	Multiple millary infarctions of brain with clinical history of cerebral episodes, including transient hemiplegia
2 ♀ 55	Emotional, periods of confusion, attacks of numbness of right arm, terminal coma	None	Considerable excess of cerebrospinal fluid	Hemorrhage 2 cm in diameter in left cerebral hemisphere, multiple capillary hemorrhages	Numerous millary infarcts	Foci of gliosis perivascular cuffings	Numbness of right arm referable to hemorrhage of left cerebral hemisphere, marked cerebral symptoms during life, with much destruction of brain, negative objective results of neurologic examination
3 ♂ 50	Convulsions followed by deep coma 2 mo before death, intense restlessness, confusion, delirium	None before convulsion, then left Babinski sign	No comment	Numerous small, spotty hemorrhages, widespread capillary hemorrhages	Numerous millary infarcts	Perivascular cuffings, foci of astrocytes	Convulsions and abnormal mental state during life hemorrhages and infarcts in cerebrum, objective results of neurologic examination negative despite much cerebral damage
4 ♂ 22	Paralysis right side (4 mo before death), then restlessness, convulsions, bright red blood in cerebrospinal fluid	Residual right hemiplegia	No comment	Large hemorrhage in right internal capsule, rupture into ventricles, multiple capillary hemorrhages	Old large infarct in cerebrum, numerous millary infarcts		Extensive cerebral destruction
5 ♂ 27	Severe occipital headaches 10 wk, drowsiness 1 mo before death	None	Flattening of convolutions due to edema	Capillary hemorrhages		Foci of glial cells in cortex, perivascular cuffings	Severe headaches before death, edema of brain at autopsy
6 ♂ 22	Severe headaches 1 wk, terminal staggering, coma		Swelling of brain	Large hemorrhage of left hemisphere with rupture into ventricles			Negligible cerebral symptoms until final episode of large hemorrhage, causing death
7 ♂ 52	Transient coma, attacks of severe headache, convulsions over 23 mo, terminal sudden coma with convulsions	Persistently negative	No comment	Large hemorrhage in cerebellum, rupture into ventricles, subependymal hemorrhages of lateral ventricle	Multiple millary infarcts	Perivascular cuffing	Recurring transient cerebral attacks ending by large cerebral hemorrhage, multiple small infarcts also found in cerebrum

8 ♂ 20	492	Severe headaches 8 mo , with nausea and vomiting, episodic confusion	Negative	Widened gyri, narrowed sulci due to increased pressure	Petechial throughout brain	Multiple milary	Severe headaches with episodic confusions and edema of brain, with multiple hemorrhages
9 ♂ 54	144	Drowsiness 9 mo , olfactory and visual hallucinations, episodic confusion, disturbing dreams	Negative	Flattened convolutions due to edema	Capillary in arachnoid	Multiple milary	Severe recurring cerebral attacks during life, with widespread cerebral destruction at autopsy
10 ♂ 55	285	Failing memory, sudden stupor and death	No comment	No comment	None	None	Little clinical cerebral disturbance, no destructive cerebral lesions at autopsy
11 ♀ 47	126	No definite symptoms	Negative		Postoperative streptococci meningitis, many capillary hemorrhages		
12 ♂ 57	116	Episodes of staggering and vertigo, severe headaches with nausea and vomiting, attacks of confusion	Bilateral Babinski sign	No comment		Multiple milary	Severe episodic cerebral symptoms with many milary infarcts at autopsy
13 ♂ 56	12	Occipital headaches 1 yr , recurring convulsions	Negative	No comment	Capillary	Multiple milary	Recurring convulsions during life, multiple small cerebral infarcts at autopsy
14 ♀ 41	192	Violent headaches, clouded, stuporous mental state 1 mo before death	Negative	Grade 2+	Capillary, multiple small subdural hemorrhages		Severe headaches and stupor during terminal illness, with edema of brain at autopsy
15 ♀ 7	86	Severe headaches, recurring convulsions, transient hemiplegia	Negative except homonymous hemianopia	Marked	None	Multiple milary, single large infarct in left cerebral hemisphere	Episodic cerebral attacks with marked cerebral destruction
16 ♂ 65	101	Failing memory, severe headaches, periodic delirium, intense restlessness	Negative	Increased amount of cerebrospinal fluid	Multiple, spotty	Multiple milary	Episodic cerebral attacks with marked cerebral destruction
17 ♂ 47	116	Weakness of left leg, attacks of headaches with vertigo, nausea and vomiting, personality change, terminal convulsion and coma		Flattened convolution and narrowed sulci	Multiple, spotty, sub-arachnoid hemorrhage in right parietal area	Multiple, small foci, large infarct of right cerebral hemisphere	Many varied cerebral symptoms with extensive cerebral destruction

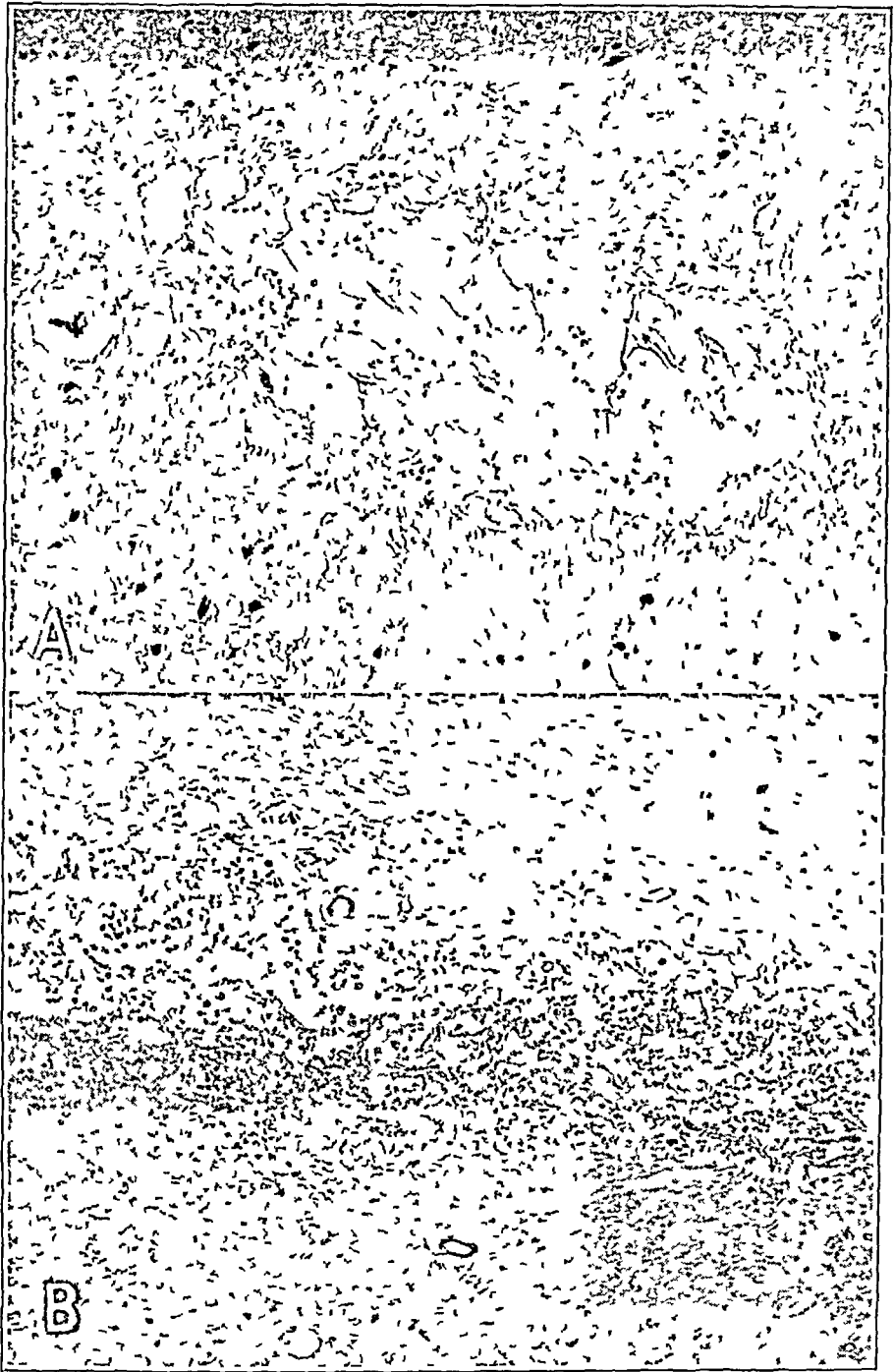


Fig 10 (case 9) —*A*, minute infarct in a section from the thalamus, showing cystic degeneration *B*, minute infarct in a section from the thalamus, showing a great number of scavenger cells Hematoxylin and eosin, $\times 50$

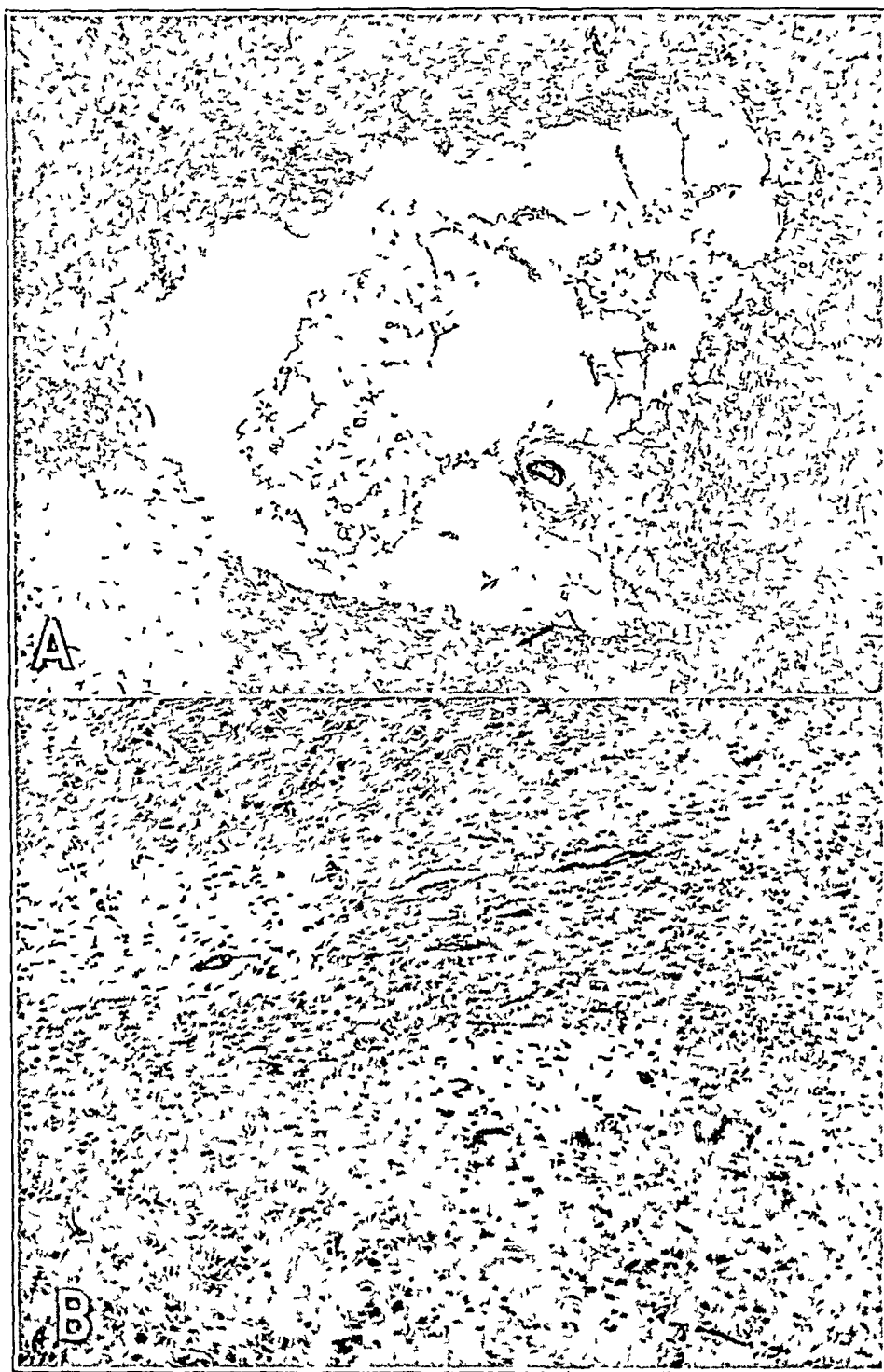


Fig 11—*A* (case 3), minute cystic cavity resulting from a small region of infarction in a section from the temporal lobe, $\times 25$ *B* (case 9), glial scar resulting from the healing of a small region of infarction in a section from the thalamus, $\times 58$ Hematoxylin and eosin

In these 17 brains, collections of lymphocytes were observed about arterioles in 10 (cases 2, 3, 5, 7, 9, 10, 11, 13, 16 and 17). These perivascular collections tended to form distinct cuffs. None of the 10 patients had serologic or other evidence of syphilis. One patient (case 4) with syphilis did not show cuffing of the cerebral vessels. For the most part these cuffings were moderate in degree (figs 13 and 14). The cuffings were not confined to the immediate neighborhood of infarction or hemorrhage. On the contrary, they were found in regions

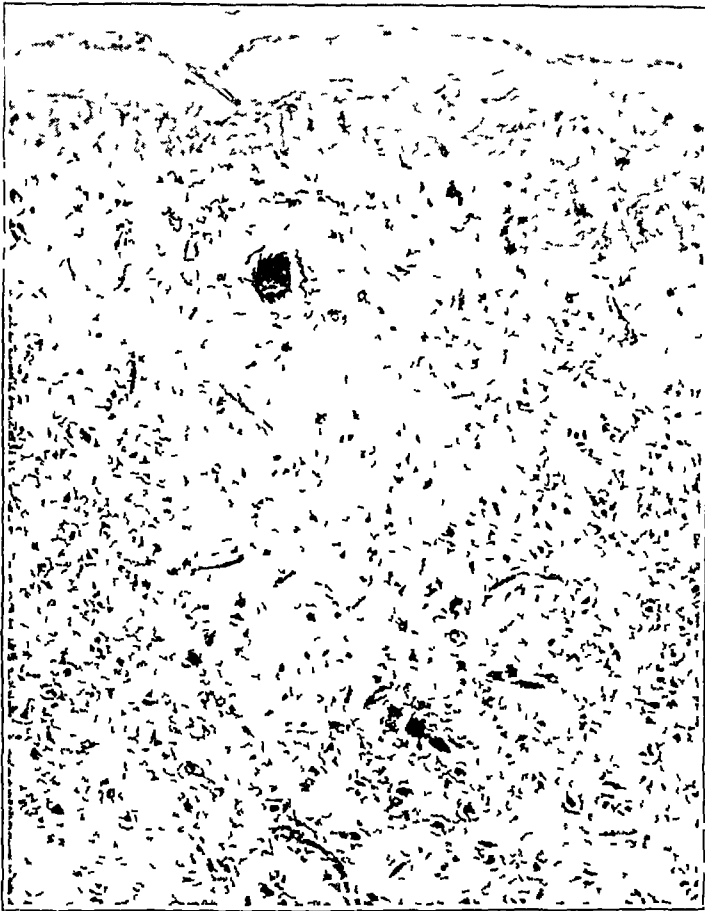


Fig 12 (case 12) —Section from the left frontal lobe, showing a zone of infarction with loss of neurons, a so-called region of devastation. Note the occluded vessel. Hematoxylin and eosin, $\times 85$.

remote from other lesions. In table 8 the occurrence of cuffing of arterioles is correlated with the presence or absence of uremia and with the nature of the other destructive lesions encountered.

Recent studies by Ecker³⁰ have shown that in some instances of encephalitis, in which periarteriolar collections of lymphocytes are

30 Ecker, A. Arsenic and the Nervous System with Special Reference to Subacute and Chronic Encephalitis, Thesis, Minnesota University Graduate School, 1938.

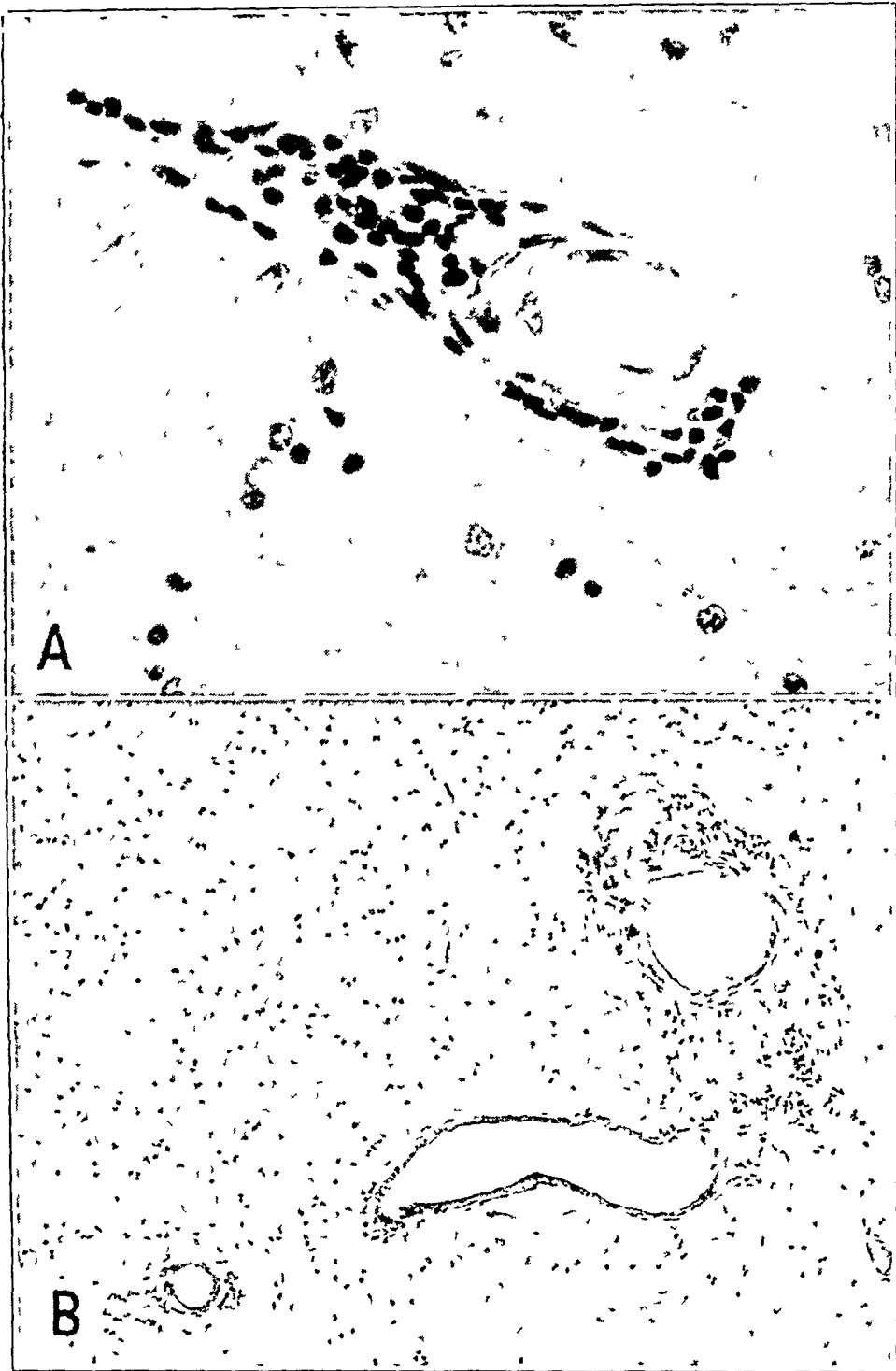


Fig 13 (case 9) —*A*, hypertrophy of the wall of a small arteriole with periarteriolar collection of lymphocytes in a section from the right occipital lobe, $\times 460$ *B*, perivascular collections of lymphocytes in a section from the thalamus, $\times 65$ Hematoxylin and eosin

found in the brain, the condition is due to arsenic. Of the 10 brains in the present series in which perivascular cuffing was present, he has analyzed 6 for the presence of arsenic (cases 2, 3, 5, 9, 11 and 13). Using the Osterberg³¹ modification of Gutzeit's test, he was unable to find arsenic in any of the 6 brains.

Case 11 ought not to be considered with the other 9 cases because of the probable relation of the cuffing to terminal meningitis, which followed operation. This, however, leaves 9 cases in which this inflam-



Fig 14 (case 13) —Meningeal arterioles, showing hypertrophied walls and perivascular collections of lymphocytes in a section from the frontal lobe. Hematoxylin and eosin, $\times 265$.

matory response was present without any apparent explanation. The occurrence of this lesion seemed not always to be an expression of a rapid course. It occurred in 1 instance (case 13) in which eighteen months elapsed between the onset of the symptoms and death, and it

31 Osterberg, A. E. A Modification of the Electrolytic Gutzeit Apparatus for the Estimation of Arsenic in Biological Material, *J. Biol. Chem.* **76** 19-22 (Jan.) 1928.

also occurred when only four months had intervened (case 3). Severe renal insufficiency was absent in 2 instances (cases 7 and 13), which indicates that this condition alone is not causative. Destructive cerebral lesions were likewise absent occasionally.

These cuffings were different in appearance from perivascular cuffings occasionally seen adjoining regions of large hemorrhage or infarction. In the latter type the cells are predominantly polymorphonuclears which are emigrating from the blood vessels into the perivascular spaces and thence into the necrotic regions, whereas the perivascular cuffings which are observed in the brains of patients dying of malignant hypertension are mainly formed by lymphocytes. The polymorphonuclear cuffings adjoining infarcts or hemorrhages are prob-

TABLE 8—*Clinical and Postmortem Observations in Cases of Malignant Hypertension in Which Cuffing of Cerebral Arterioles Occurred*

Case	Concentration of Urea, Mg per 100 Cc of Blood	Duration of Life, Months After Onset of Symptoms	Destructive Lesions in Brain
2*	134	12	Multiple hemorrhages and infarcts
3*	158	4	Multiple hemorrhages and infarcts
5*	657	13	None
7	24	17	Large hemorrhage of cerebellum
9*	144	9	Multiple hemorrhages and infarcts
10	285	12	None
11*†	126	6	Meningitis, postoperative
13*	42	18	Capillary hemorrhages, multiple infarcts
16	101	6	Multiple hemorrhages and infarcts
17	116	8	Multiple hemorrhages and infarcts

* Analysis for arsenic gave negative results

† Cuffing probably evidence of encephalitis accompanying meningitis

ably due to necrosis of tissue and correspond to the polymorphonuclear response to infarcts observed in other organs, such as the heart, kidney and lung. The periarteriolar lymphocytes in these brains affected by hypertension should probably be looked on as an inflammatory, but not necessarily an infectious, response. They may be the result of noninfectious tissue damage.

A second type of inflammatory or proliferative reaction seen in these brains was the proliferation of glial cells (fig 15). This was observed in 6 brains (cases 2, 3, 5, 9, 14 and 17). In 3 brains (cases 2, 9 and 17) dense accumulations of glial cells of all types, but mainly astrocytes, were seen in the white matter, where ordinarily but few astrocytes are seen. Small focal collections of glial cells were noted about some small vessels in 5 brains (cases 3, 5, 9, 14 and 17). No lesions resembling those of periaarteritis nodosa were found in any of the brains. It is

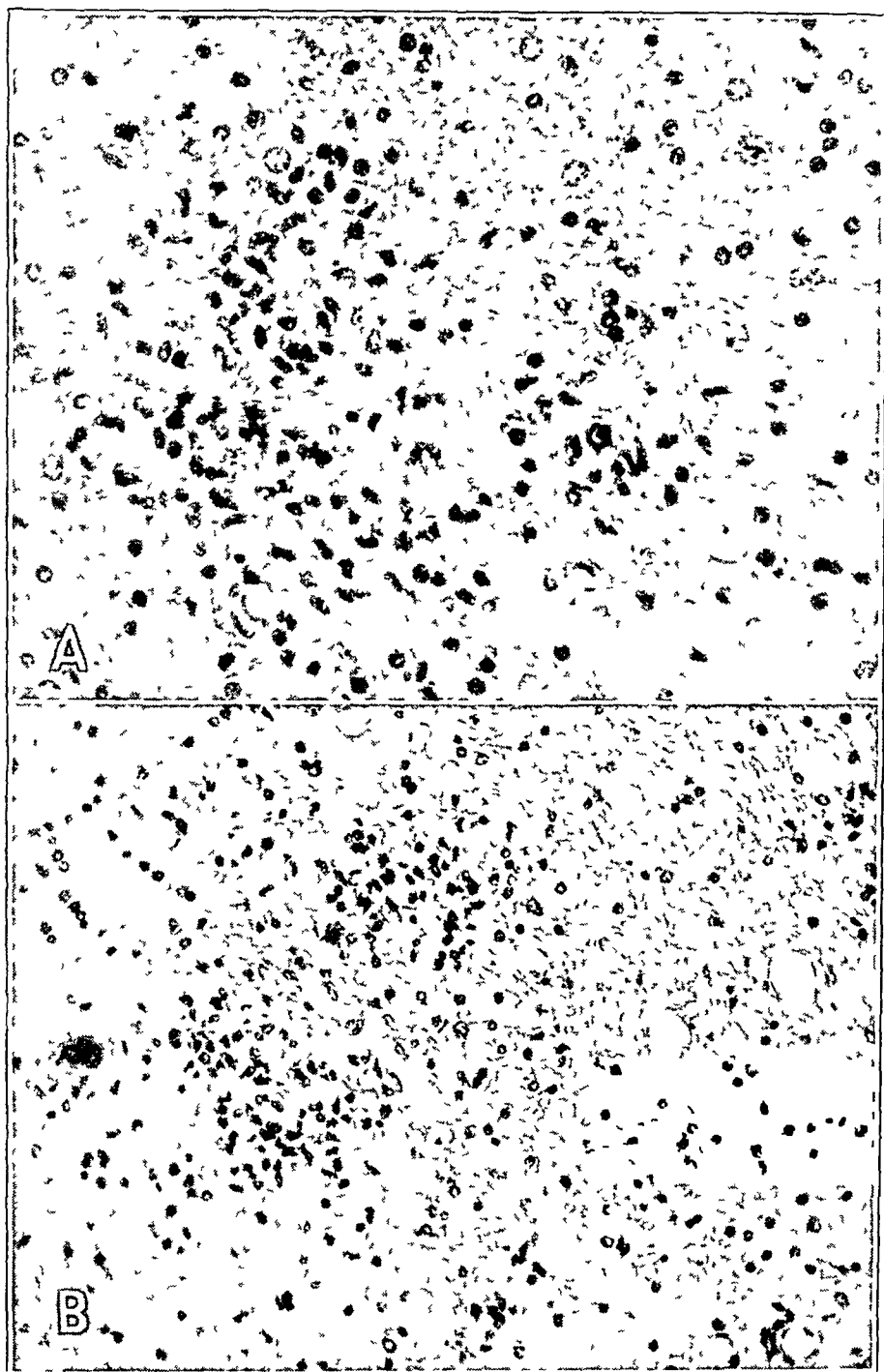


Fig 15—*A* (case 17), focal proliferation of glial cells in the white matter of a section from the left parietal region. Many astrocytes (gemastete glia) appear swollen, $\times 265$. *B* (case 9), focal proliferations of glial cells in a section from the thalamus, $\times 165$. Hematoxylin and eosin.

of interest that perivascular cuffings occurred in all but 1 (case 14) of the 6 brains in which glial proliferations were encountered (table 7)

Intracerebral and Extracerebral Edema—It is important to have information regarding edema of the brain in patients with hypertension because of the possibility of relieving symptoms of this condition during life by means of hypertonic solutions. In table 1 the available data concerning disturbances of intracranial fluids are correlated with (1) the degree of choking of the optic disks, (2) the presence or absence of uremia at the time of death and (3) the pressure of the subarachnoid fluid during life.

Brains that have been preserved in fixative solutions are not satisfactory for studying the presence or absence of edema. Consequently, my data regarding this phenomenon have been taken from the gross and microscopic descriptions of these brains as recorded at the time of the original autopsy. Edema or marked increase in the amount of cerebrospinal fluid was noted by the pathologist in 11 of the 17 cases in this series.

As one might expect, it would appear that the patients with high grades of papilledema often had an increase in the pressure of the cerebrospinal fluid and also showed edema of the brain at autopsy. No instance of "pressure cone" (such as was described by Blackfan³² in his famous case) was observed in this series.

On microscopic examination it was possible to find some apparent increase in the size of the perivascular and pericellular spaces of these brains, and in places the fiber tracts were widely separated, seemingly by edema fluid, in the form of a meshwork. It is not certain, however, whether these changes resulted from actual increase in the amount of fluid in the brains or from postmortem shrinkage during fixation.

One may conclude from the data in table 1 that intracerebral edema or an increased quantity of cerebrospinal fluid does occur often in malignant hypertension, and that either of these conditions may play a significant role in bringing about an increase in intracranial tension, thus producing symptoms. Signs of these disturbances should be watched for carefully during life, and if such signs appear measures should be instituted to combat them.

Anemia of the Brain—This condition has been discussed widely as playing a part in causation of the cerebral symptoms that so often accompany severe hypertension. It seems significant that in the autopsy records of the 17 patients no statement can be found that would indicate that an anemic condition of the brain was observed. There was no

³² Blackfan, K. D. Acute Nephritis in Children, with Special Reference to the Treatment of Uremia, *Bull. Johns Hopkins Hosp.* 39: 69-90 (Aug.) 1926.

microscopic feature that could be interpreted as being due to general anemia, and there were only such evidences of local anemia as the infarcts³³

33 Dr H P Wagener stated "The average ratio of wall to lumen in normal retinal arterioles which measure 66 to 116 microns in diameter ophthalmoscopically is variously stated as from 1/4 to 1/7. Thus the retinal arterioles present a closer similarity in thickness of wall to the cerebral arterioles than to the arterioles of the peripheral muscles

With reference to the collections of lymphocytes around the arterioles. Periarteriolar sheathing of the retinal arterioles is found in a certain number of cases of hypertension. It has seemed to me that this occurs mainly in patients who have or have had retinitis. In this event no doubt the lesion represents the emigration of leukocytes from the vessels in the neighborhood of infarcts or of areas of edema of the retina. However, it may be possible that the lymphocytic cuffing that Dr Rosenberg found about the arterioles at a distance from the infarcts in certain brains may explain the localized periarteriolar sheathing in some cases in which existence of retinitis, past or present, cannot be definitely demonstrated

With reference to vasospasm and destructive changes, transient loss of vision in one eye or in a sector of an eye does occur at times presumably on the basis of arteriolar spasm. In such cases, when seen during the attack, the main arteriole leading to the affected quadrant is invisible since it is empty of blood, and its walls, being of normal thickness and structure, are invisible or transparent. In such cases, the loss of vision never lasts for more than five minutes. If the loss of vision persists for a period longer than five minutes, an ischemic infarct of the affected portion of the retina can be seen ophthalmoscopically and vision is permanently reduced to a greater or lesser degree, usually greater. In some of these cases, after subsidence of the acute picture of the infarct, the arteriole can be seen to be definitely thrombosed. In other instances, however, the arteriole shows only generalized narrowing, irregularities in lumen and evidence of thickening of the walls, which can be spoken of as postspastic sclerosis. It is certain that in these instances there is a "destructive" lesion in the retina (an infarct with necrosis?), but it is not known whether there is necessarily primary thrombosis of the arteriole or whether the thrombosis, when present, or the residual structural changes in the walls of the arterioles are secondary to the vasospasm, as is the infarct

In the more usual type of "spasm" of the retinal arterioles, seen for example in toxemia of pregnancy, retinitis does occur in the absence of ophthalmoscopically demonstrable structural changes in the walls of the main arterioles—the visible localized "angiospastic" narrowings at times disappearing and leaving an apparently normal arteriolar wall within twenty-four hours. However, on microscopic study it is possible to demonstrate in certain instances the closure of minute arterioles (20 microns or less in diameter) leading to the region of the cotton wool patch, or infarct (Friedenwald, J S. *The Pathology of the Ocular Changes in Nephritis and Hypertension*, in Berglund, H, and Medes, G. *The Kidney in Health and Disease*, Philadelphia, Lea & Febiger, 1935, pp 638-664), and the question arises, as it does regarding the brains that Dr Rosenberg examined, whether such a small vascular occlusion must be present in the case of all infarcted foci or whether the apparent infarct or necrosis can be produced by the anoxemia of the tissues attributable to the spasm alone. In the case of the retinal infarcts, Friedenwald concluded that the occlusive changes in the terminal arterioles were due to hyaline lipid degeneration rather than to thrombosis"

RELATION OF SYMPTOMS TO LESIONS

The histories of the 17 patients with malignant hypertension have been reviewed in an attempt to correlate the cerebral symptoms that were suffered during life with the type of pathologic changes encountered in the brain at autopsy

In his book published in 1915 Allbutt³⁴ carefully considered the cause of transient or "larval" forms of cerebral episodes which occur in association with hypertension. He was well informed on the literature dealing with these attacks, and after marshaling the evidence for the functional hypothesis (vasospasm) and for the organic origin, he was obliged to assume that in the vast majority of cases transient pareses in persons with hyperpiesia and chronic renal disease signify small cerebral hemorrhages

Oppenheimer and Fishberg³⁵ reviewed the subject of the acute episodes of cerebral phenomena that occur in association with various hypertensive states and independent of uremia. Although at that time they did not report any studies of their own pathologic material, they stated that anatomic examination of the brain of a person who has succumbed after having had these acute manifestations does not reveal any focal lesions to account for the epileptiform convulsions and other symptoms, such as coma, headache, amaurosis, hemiplegia and aphasia, which are so striking during life. They stated that such brains show only inconstant edema or anemia, and because of the paucity of anatomic changes they felt it necessary to seek the pathogenesis of "hypertensive encephalopathy" (as they named the condition) along functional lines. They concluded that the syndrome is due primarily to hypertension and that vasospasms are directly responsible. They were in agreement with Volhard and Fahr,¹ who asserted that these phenomena are not due simply to renal insufficiency.

It would seem apparent from the literature that undoubtedly there have been cases of hypertension in which cerebral symptoms were present during life and in which at necropsy no actual focal lesions could be demonstrated. However, in this study of the brain in malignant hypertension, it was always possible to demonstrate regions of cerebral destruction when focal cerebral symptoms had been present during life, and in instances in which the brain showed no destructive lesions (cases 5, 10 and 14) the history revealed that episodic focal cerebral symptoms

34 Allbutt, T. C. *Diseases of the Arteries, Including Angina Pectoris*, London, Macmillan & Co., 1915

35 Oppenheimer, B. S., and Fishberg, A. M. *Hypertensive Encephalopathy*, *Arch Int Med* **41**:264-278 (Feb) 1928

had not been present during life. The present study indicates that when focal cerebral symptoms occur during the terminal illness destructive lesions in the brain are frequently present. A recent paper by Davison and Brill³⁶ gives emphatic support to this observation.

The case reported recently by me in collaboration with Drs. Keith and Wagener²⁹ is of special interest in this connection. Severe hypertension developed. The course of the disease was rapid, and the terminal phase was so violent as to be termed by us "explosive." During the final days of the illness there were many bizarre symptoms and findings which appeared to be evidence of a cerebral disturbance. At the time of our original studies, we found no destructive lesions in the brain. We have, however, recently reviewed this case thoroughly in the light of pathologic observations in the present series. In studying many more microscopic preparations from various cerebral regions, we have encountered three exceedingly minute microscopic foci of infarction, but no other lesions. It seems to us that one would not be justified in attributing the many striking cerebral symptoms to these minute lesions.

A PROPOSED CLINICOPATHOLOGIC CLASSIFICATION OF THE CEREBRAL PHENOMENA OF SEVERE HYPERTENSION

After a review of the clinical and pathologic data at my disposal, it appears that three primary types of cerebral symptoms occur in malignant hypertension: (1) symptoms of increased intracranial pressure, (2) symptoms of multiple military cerebral lesions and (3) symptoms of large cerebrovascular accidents. Symptoms of any one of these three groups may occur alone, and all combinations of them are seen. Accordingly, a fourth group, mixed types, may be distinguished.

Increased Intracranial Pressure—The symptoms that result from intracerebral and extracerebral edema are those of increased intracranial pressure and include severe headaches, nausea and vomiting, mental dulness and drowsiness. At necropsy more or less severe arteriolar thickening and narrowing of the lumen of the vessels were noted in these instances of edema, but no destructive lesions of the brain tissue could be found. This simple type occurred in 2 cases (5 and 14) in my group. The following case history is typical.

CASE 14—A housewife, aged 41 years, was first seen in May 1935, when high blood pressure was discovered. At that time she complained of severe, migraine-like headaches and blurring of vision on stooping. Physical examination revealed

³⁶ Davison, C., and Brill, N. Q. Essential Hypertension and Chronic Hypertensive Encephalopathy (a Clinico-Pathologic Study), *Ann Int Med* **12** 1766-1781 (May) 1939.

accentuation of the aortic second sound. At that time her blood pressure was recorded on several occasions as follows: 220 systolic and 125 diastolic, 184 systolic and 120 diastolic, and 196 systolic and 120 diastolic. Examination of the fundus showed retinal arteriosclerosis of grade 1 to 2 on a basis of 1 to 4, slight generalized narrowing and one small streak hemorrhage below the right disk. The urine did not contain albumin or casts. During the succeeding year the patient was seen occasionally because of spells of faintness, shortness of breath and precordial pain. The blood pressure was always found to be elevated.

On April 16, 1936, she was admitted to the hospital. Her condition was serious. There were marked shortness of breath and a sense of substernal pressure. She had been vomiting frequently for three weeks, had been having frequent nosebleeds and was extremely weak.

Examination revealed a peculiar pallor, which was interpreted as being due possibly to vasospasm of the arterioles of the skin. There was narrowing of the retinal arterioles, grade 2 plus, and sclerosis, grade 3. There was edema of the upper nasal margins of both disks, with an elevation of 1 D. Many hemorrhages were present in the retina of the right eye. Edema was present over the sacrum, and there was evidence of fluid in both pleural cavities. The heart was enlarged. There was marked tenderness over the liver. Severe hypertension was present and continued to within a few days of death (fig. 1).

The urine contained albumin, grade 3. The level of blood urea was 64 mg. per hundred cubic centimeters. The value for hemoglobin was 10.7 Gm. The erythrocytes numbered 3,530,000 and the leukocytes 10,500 in each cubic millimeter of blood. A roentgenogram of the chest revealed enlargement of the heart, passive congestion and fluid at the bases of both lungs. The electrocardiogram showed left ventricular preponderance and inverted T waves in derivation 1. T waves in derivation 2 were isoelectric.

During the succeeding days progressive evidence of renal and cardiac insufficiency developed. In the hospital the patient had severe headaches, often accompanied by nausea and vomiting. A lumbar puncture was performed, the initial pressure being 8 cm. of water and the response to pressure over the jugular veins being prompt. The cell count was 2 per cubic millimeter. The value for proteins in the fluid was 30 mg. per hundred cubic centimeters. It was necessary to remove fluid from both pleural cavities on several occasions. On May 15, 1936, the patient was stuporous. On the following day Cheyne-Stokes respirations were present, and she was in a state of semicoma. The reflexes remained equal on the two sides, and there was no evidence of paralysis. On May 20 a pericardial friction rub disclosed the presence of pericarditis. During the next month her state of consciousness varied, at times she was fairly clear mentally, often she was stuporous. Coma was present for about twenty-four hours before death, which occurred on June 22.

From the time of onset of the symptoms until death only thirteen months had elapsed. At the time of death, the value for blood urea had risen to 192 mg. per hundred cubic centimeters, for creatinine it was 4 mg. and for serum sulfates it was 12.2 mg. At autopsy the following significant diagnoses were made: hypertrophy of the heart (530 Gm., normal 275 Gm.), dilatation of the left ventricle, grade 2 plus, atrophy of the kidneys (237 Gm., normal 275), of arteriosclerotic type, multiple infarcts and abscesses of the lungs with organized thrombosis of the pulmonary vessels and unresolved bronchopneumonia, hydrothorax (1,000 cc. right side, 2,000 cc. left side), ascites (200 cc.), edema of the legs, grade 2, resolving fibrinous pericarditis, and arteriosclerosis of the aorta, cerebral arteries and coronary arteries—all grade 1.

The brain weighed 1,230 Gm. Beneath the dura, in the epiarachnoid space, were several regions of petechial hemorrhage, each surrounded by a narrow zone of brownish pigment. The brain appeared to be definitely edematous. Arteriosclerosis of the vessels at the base of the brain was graded 1.

There was microscopic evidence of edema of the brain, and small capillary hemorrhages were present in a section from the parietal cortex. Infarctions were not encountered in either the gross or the microscopic examination. Several small vessels were surrounded by dense collections of glial cells. Rather marked medial thickening was encountered in the arterioles of the cortex, but the vessels of the meninges and those of the medulla and the hypothalamus appeared to be only slightly thickened. The internal elastic lamina also appeared to be slightly thickened. Determinations of the ratio of the lumen to the wall of the cerebral arterioles showed reduction only in the cortical vessels.

Marked cardiac and some renal insufficiency developed in a 41 year old woman with severe hypertension. For one month before death she was in a peculiar mental state varying constantly between stupor, semicomatose and mental alertness. At times she could obey only simple commands. At other times she was in control of her senses. These symptoms, together with headache, nausea and vomiting, suggested that increased intracranial pressure was present, probably due to edema of the brain. In spite of these clinical phenomena, and in spite of the fact that definite edema of the brain was observed at autopsy, lumbar puncture showed normal pressure readings of the cerebrospinal fluid during life. The outstanding lesion in the brain at autopsy was edema.

Multiple Miliary Destructive Lesions—When the brain has suffered widespread multiple miliary infarctions or hemorrhages or both, a wide variety of symptoms results, usually these symptoms are evidence of injury to localized cerebral regions. The region of the brain which is destroyed or injured often is not large enough to cause disturbances in reflexes or in sensations or motor power, and the results of neurologic examinations are accordingly usually found to be objectively negative. In 1 instance of this type there occurred episodes of vertigo and staggering, suggesting damage to the equilibratory system, in another, olfactory hallucinations occurred, suggesting injury to a region of the hippocampus. Transient hemiplegias and aphasias are not infrequent, and these suggest lesions in the great projection systems of the cortex. Personality changes suggest damage to the frontal lobes. The observation of many small cortical lesions provide an explanation for the occurrence of convulsions in some of these cases. Cases 2 and 3 represent fairly simple examples of this second type, in which symptoms of focal cerebral disturbance are associated with multiple small destructive lesions of the brain. Case 3 is presented.

CASE 3—A musician, aged 50 years, came to the Mayo Clinic on Jan 27, 1927, complaining of shortness of breath for four months. Swelling of the ankles and distention of the abdomen had been present for two weeks.

Examination showed orthopnea and enlargement of the heart. There was accentuation of the pulmonic second sound. Peripheral arteriosclerosis was graded 2. There were ascites and edema of the lumbosacral regions and of the legs. Rales were heard over the bases of both lungs. Results of the gross neurologic examination were negative. Examination of the fundi revealed sclerosis, grade 2, of the retinal arteries, with flame-shaped hemorrhages and numerous cotton wool exudates characteristic of the retinitis of malignant hypertension. Edema of the optic disks was present, with elevation of 1 D. The blood pressure was 220 mm of mercury systolic and 140 mm diastolic.

There was a trace of albumin in the urine. The concentration of hemoglobin (Dare) was 72 per cent, erythrocytes numbered 4,000,000 and leukocytes 16,800 in each cubic millimeter of blood. The blood urea measured 124 mg per hundred cubic centimeters and the creatinine 5 mg. The electrocardiogram showed inversion of the T wave in all three leads.

Two days after the patient's admission to the hospital a severe generalized convulsion suddenly developed, during which he bit his tongue. For a short time he was pulseless and in deep coma, the pulse then returned but for some minutes was rapid and of poor quality. During this period his respirations were stertorous. Venesection was performed, during which procedure he roused and became perfectly rational, talked and moved all extremities. One and a half hours later he had another generalized convulsion. After the second convulsion a Babinski sign could be elicited in the left foot, but tendon reflexes were equal on the two sides and no paralyses were noted.

In the succeeding weeks the patient had periods of marked restlessness with a peculiar personality change. He refused to follow instructions, insisted on getting out of bed, stole ice and water from other patients and drank the water intended for washing his teeth. During the next month edema and ascites increased.

On March 6 he became comatose and died. At the time of death the blood urea was 158 mg per hundred cubic centimeters and the creatinine 5.3 mg.

At autopsy the following significant diagnoses were established: hypertension with hypertrophy of the heart (870 Gm), hydrothorax of the left cavity (1,000 cc) and chronic diffuse nephritis.

Atherosclerosis in the vessels at the base of the brain was graded 3. On sectioning the brain, there were seen many small, scattered regions of hemorrhage (the largest of which was 1.5 cm in diameter) and numerous small regions of infarction, some of which had formed cavities or cysts. The largest infarct was 8 mm in diameter.

Microscopically, a mild degree of thickening was noted in the arteries and arterioles of the subarachnoid space. In the parenchyma of the brain proper the walls of most of the arterioles were also definitely thickened. Some arterioles were entirely obstructed by thrombi, and a canalized thrombus was observed in one of them. Many of the cerebral arterioles showed well marked cuffing with lymphocytes. The regions of infarction were noted to be of various ages, many showed scavenger cells and blood pigment. Swollen astrocytes were noted in the vicinity of some infarcts, and about these the adjoining brain tissue was densely infiltrated with various glial cells. Occasional minute capillary hemorrhages were present.

The internal elastic lamina of arterioles was in many instances proliferated and thickened, giving the picture of so-called elastosis, with many fibers of elastic tissue infiltrating and ramifying in the various layers of the wall. Capillary hemorrhages were found in the hypothalamic region, in the cortex and in the medulla.

A man aged 50 years had severe hypertension and heart failure. During the last months of his life he had convulsions, periods of coma and of marked restlessness and personality changes, followed by delirium and terminal coma. In the brain were observed multiple regions of destruction due to hemorrhages and infarcts.

Large Cerebrovascular Accidents and Mixed Types of Cerebral Symptoms—The phenomenon of a large cerebrovascular accident is well known and deserves no special comment here, except to state that such an accident may follow in the course of either of the aforementioned varieties of clinical course. Thus, a patient the course of whose illness indicated that he has suffered multiple focal destructive cerebral lesions may suddenly show evidences of a large cerebrovascular accident and die. The following case is illustrative of such a course.

CASE 1—A woman 45 years of age registered at the Mayo Clinic on Aug 26, 1921. Six months previously she had had a "stroke," followed by partial paralysis of the right side, at which time her systolic blood pressure was 280 mm of mercury. Paralysis cleared gradually. For two months vision had been failing. She had lost 75 pounds (34 Kg). For two weeks she had had acute attacks of tinnitus and had noted impairment of memory and vertex headaches. Her mental state was clouded. Since her first stroke she had been emotionally unstable and had expressed many ungrounded fears. Examination showed dyspnea and edema of the ankles. The heart was enlarged. Its action was regular. The aortic second sound was accentuated. The results of the gross neurologic examination were negative. Peripheral arteriosclerosis was graded 2. The blood pressure was 240 mm of mercury systolic and 120 mm diastolic.

There were several small conjunctival hemorrhages in the right eye. Papilledema was present, with an elevation of 1 D in the left eye and 3 D in the right eye. There was sclerosis of the retinal arteries and irregular narrowing of their caliber. Massive exudates and extensive hemorrhages were noted along the vessels, and beginning macular stars were observed.

The urine contained only a trace of albumin and occasional casts. The concentration of hemoglobin (Dare) was 82 per cent, erythrocytes numbered 5,110,000 and leukocytes 13,000 in each cubic millimeter of blood. The value for blood urea was 34 mg per hundred cubic centimeters, and that for creatinine 1.9 mg. The specific gravity of urine varied from 1.000 to 1.026.

On the third day after admission the patient suddenly became unable to speak, and left hemiplegia appeared. She lapsed into coma, Cheyne-Stokes respirations developed, and she died two days later.

At autopsy the following significant diagnoses were made: cerebral hemorrhage, chronic diffuse nephritis, hypertrophy of the heart (400 Gm, normal 250 Gm), early bronchopneumonia and chronic passive congestion of the lungs.

Grossly, the right hemisphere of the brain presented a large cavity, 2 by 5 cm in diameter, involving the corpus striatum and the internal capsule. This cavity was filled with blood, and blood had ruptured into the ventricles. Scattered about the surface of the cerebrum and cerebellum were numerous hemorrhages beneath the pia. There was sclerosis, grade 2 to 3, of the large vessels at the base of the brain. No gross evidence of infarction was noted.

Microscopic examination showed that the wall of the large hemorrhagic cavity was not organized. The cerebral hemorrhage had obviously occurred within a few hours preceding death.

Sections from the parietal regions of the cortex, from the hypothalamus and from the region of the pons showed numerous small regions of infarction. These were too small to have been seen grossly, but those in the brain stem might easily have interrupted important fiber tracts. Many of these minute infarcts were old, perhaps having occurred some months before death. This fact was shown by the presence of degenerated blood pigment in the walls of the cavities and in the adjoining brain tissues.

There was marked thickening of the arteriolar walls in many of the regions studied.

A 45 year old woman came to the clinic with a history of transient partial hemiplegia of six months' duration. She had been in a peculiar mental state and had many bizarre symptoms, including emotional instability, tinnitus and impaired memory. In spite of this history, the objective results of a careful neurologic examination were negative. A large cerebral hemorrhage caused her death. At autopsy, in addition to the large hemorrhage, multiple minute regions of destruction were observed throughout the brain.

A further variety of the mixed type which may be encountered is exemplified in the following history of a patient the course of whose illness suggested that widespread military destructive lesions had occurred and who showed terminal clinical evidence of edema of the brain in the form of signs of increased intracranial pressure.

CASE 9—On July 5, 1934, a physician, 54 years of age, came to the clinic complaining of a loss of weight of 38 pounds (17.2 Kg) and of malaise and drowsiness, together with marked thirst and polyuria, of about nine months' duration. Two months before his arrival he had experienced olfactory hallucinations, and since that time he had had bouts of nausea and vomiting. He had noted some shortness of breath on exertion, and during the preceding two months severe parietal headaches and insomnia had been very troublesome. He had become mentally dull, and for one month his vision had been failing. During this month he had had visual and auditory hallucinations. He complained of seeing grotesque objects and of hearing voices.

On examination he appeared anemic. Palpable peripheral vascular sclerosis was graded 3 plus. The heart was enlarged, and the aortic second sound was accentuated. The blood pressure varied between 160 and 210 mm of mercury systolic and 110 and 140 mm diastolic. The retinal arteries were narrowed and sclerosed. There was retinitis, characterized by the presence of hemorrhages and cotton wool exudates. The nasal margin of the right disk was edematous.

The urine contained albumin and occasional casts, together with erythrocytes and a few pus cells. The value for hemoglobin was 14.5 Gm per hundred cubic centimeters, erythrocytes numbered 3,830,000 and leukocytes 7,000 in each cubic millimeter of blood. Blood urea was 98 mg per hundred cubic centimeters and creatinine 2 mg. The electrocardiogram showed left ventricular preponderance and inverted T waves in lead I. T waves in lead II were diphasic.

In the hospital the patient continued to be nauseated and vomited a great deal. Cheyne-Stokes respiration appeared. He became more confused and was troubled by disturbing dreams and thoughts. A gallop rhythm developed, the heart beat became irregular, and rales appeared in the bases of the lungs. The liver was enlarged. The patient became stuporous, slipped into coma and died on Aug 7, 1934. His blood pressure remained above 200 systolic and 130 diastolic until the day before death. At the time of death the urea of the blood had risen to 144 mg per hundred cubic centimeters and the creatinine to 5.2 mg. Thus, clinically he presented a picture of terminal cerebral, retinal, cardiac and renal failure.

At necropsy the following significant diagnoses were made: cardiac hypertrophy (651 Gm, normal 300 Gm), granular kidneys, infarcts of the brain, arteriosclerosis of the aorta, grade 2 plus, edema and congestion of the lungs, and organized bronchopneumonia.

The brain weighed 1,640 Gm. Gross examination revealed flattening of the convolutions, due to edema. Sclerosis of the large cerebral vessels was graded 3. On sectioning the brain numerous small infarcts were seen throughout the white matter of the cerebrum and in the basal ganglia. These measured from 2 to 5 mm in diameter.

Microscopic examination revealed multiple miliary infarctions throughout the brain. These were found in various sections of the cortex, in the white matter and in the basal nuclei. The infarcts varied in age, fresh infarcts were associated with many scavenger cells and degenerating nerve cells, older ones with many gemastote astrocytes and fewer scavenger cells. Infarcts were found with glial fibers only where brain tissue had been replaced, these were obviously very old. Some infarcts took the form of small cystic cavities with much old blood pigment deposited in the walls. Small capillary hemorrhages were encountered in the arachnoid and in some sections of the cortex. In sections from the frontal cortex dense collections of astrocytes and marked glial fibrosis were observed. Numerous arterioles in these regions showed cuffing with lymphocytes. Many nerve cells in the frontal lobes were degenerated, and around these cells were collected large numbers of oligodendroglial cells. There was definite microscopic evidence of edema. It was believed that the increase in weight of the brain was due in part to the edema and in part to the gliosis.

The arterioles throughout various sections of the cerebral cortex showed moderate thickening of walls, due to increase in size and number of cells of the media—medial hypertrophy. Some vacuolar change was observed in the medial coat of a few arterioles. No other evidence of degeneration or necrosis was seen in the arterioles in any sections examined.

Severe hypertension developed in a 54 year old physician. During the last three months of his life severe symptoms of increased intracranial pressure and cerebral damage appeared in the form of violent headaches, mental dulness, olfactory, visual and auditory hallucinations and, finally, confusion, disturbing thoughts, terminal stupor and coma. At no time during life was any evidence of paralysis noted, and convulsions did not occur. At autopsy, arteriolar changes were only moderately advanced in the cerebral cortex, and slight degrees of thickening were observed in the basal ganglia and brain stem. The brain was unusually heavy, probably owing to edema and gliosis of the

cerebrum An indeterminate amount of the cerebral substance was entirely destroyed by small macroscopic and countless microscopic infarctions of varying ages

COMMENT

Seventeen brains from patients who had died of malignant hypertension have been surveyed as a basis for this study. Destructive cerebral injuries were noted in 12 brains, or 71 per cent, a remarkably high incidence. As a result of comparison of the clinical data and the lesions in the brain noted at autopsy, it appears that the cerebral syndromes that occur in patients with malignant hypertension may be divided into various types. For each type characteristic pathologic changes are found. The primary types of cerebral lesion responsible for symptoms appear to be (1) intracerebral and extracerebral edema, (2) multiple military destructive lesions, that is, hemorrhages or infarcts or both, and (3) large destructive lesions. In the interest of more exact diagnosis and better understanding of this neurologic phase of hypertension, some such classification should be attempted for every patient with hypertension presenting symptoms of cerebral disturbance.

In the past many of the clinical phenomena occurring in these patients were attributed to spasm of cerebral vessels. These spasms may indeed occur and perhaps are responsible for the lesions. However, it would appear that such an assumption may lead the clinician to an unjustified sense of security concerning the brain. A history of focal cerebral symptoms in these cases of malignant hypertension was found to be associated constantly with more or less widespread cerebral destruction when the brain was examined carefully after death. This study would seem to indicate that in the future those who maintain that these symptoms occur in the absence of destructive lesions must examine the brain carefully. Rosenblath³⁷ offered an explanation for the occurrence of these symptoms in episodes. He expressed the opinion that each attack is due to the occurrence of one or more new foci and perhaps to increase in size of the original ones. In the light of the observations in my own review, the latter suggestions appear to be tenable.

CONCLUSIONS

- 1 The cerebral arterioles are profoundly altered in patients with malignant hypertension. The alteration takes the form of an increase in the thickness of the walls with reduction of the caliber of the lumens, such as has been found in many other viscera of patients with this disease.

³⁷ Rosenblath. Ueber die apoplektiforme, nicht embolische und vorwiegend unblutige Hirnerweichung und über "Arterio-Capillary Fibrosis" *Ztschr f klin Med* **106** 482-527, 1927.

2 The brain is frequently seriously injured by vascular lesions in patients with malignant hypertension

3 Patients with malignant hypertension whose clinical course suggests that cerebral injury has occurred can be divided into distinct groups on the basis of the nature of these symptoms, and for each group a characteristic pathologic picture can be inferred with considerable accuracy

4 Transient cerebral phenomena of malignant hypertension that have previously been designated by terms such as "cerebral crisis" or "hypertensive encephalopathy" and ascribed to vasospasm may often be associated with widespread destructive cerebral lesions

RENAL INFARCTION

STATISTICAL STUDY OF TWO HUNDRED AND FIVE CASES AND DETAILED REPORT OF AN UNUSUAL CASE

HAROLD J HOXIE, M D
AND
CHARLES B COGGIN, M D
LOS ANGELES

Despite the fact that renal infarction has been thoroughly studied experimentally¹ and described in detail from the pathologic and clinical points of view,² it has rarely been diagnosed correctly during life. This is because in the majority of cases there are no symptoms. When clinical symptoms and signs do appear, they are alarming and produce difficulties in differential diagnosis which may result in the performance of unnecessary surgical procedures.

We have recently observed an unusual case of renal infarction with hemoglobinuria and uremia. This has stimulated us to review a group of autopsy records.

STATISTICAL STUDY

Review of the protocols of 14,411 autopsies performed at the Los Angeles County Hospital during the past nine years revealed that renal infarcts were present in 205 patients, an incidence of 1.4 per cent. The tiny pitted scars characteristic of renal arteriosclerosis were not included as infarcts. The presence of renal infarcts was diagnosed clinically in only 2 of the patients.

The ages of the patients ranged from 4 months to 88 years. Five of the patients were infants less than 1 year of age. One eighth of the patients were under 30 years of age, and a little more than half were over 50. The ratio of males to females in the group did not differ significantly from that in the entire series.

From the Department of Medicine of the College of Medical Evangelists and the Los Angeles County Hospital.

1 Karsner, H. T., and Austin, J. H. Studies in Infarction, *J. A. M. A.* **57**: 951-958 (Sept. 16) 1911.

2 (a) Desjacques, R., and Boijeau, A. Les gros infarctus du rein, *Lyon chir.* **33**: 645-674 (Nov.-Dec.) 1936. (b) Schildt, E. Ueber den aseptischen, embolischen Niereninfarkt, *Acta chir. Scandinav.* **70**: 299-352, 1933. (c) Lemierre, A. Sur un cas d'infarctus rénal, *Prat. med. franç.* **13**: 711-724 (Oct., B) 1932. (d) Barney, J. D., and Mintz, E. R. Infarcts of the Kidney, *J. A. M. A.* **100**: 1-6 (Jan. 7) 1933. (e) Danhez, P. Les grands infarctus rénaux, *J. d'urolog.* **23**: 481-495 (June) 1927. (f) Folsom, A. I., and Alexander, J. C. Total Infarction of Right Kidney. Fibrotic Atrophy of Left Kidney, Case Presentation, *Urol. & Cutan. Rev.* **38**: 197-198 (March) 1934. (g) Schwartz, J. Renal Infarcts. Surgical Aspect of Bacterial Endocarditis, *Am. J. Surg.* **39**: 70-76 (Jan.) 1938. (h) Aschner, P. W. The Clinical Importance of Aseptic Infarction of the Kidney, *Am. J. M. Sc.* **164**: 386-401 (Sept.) 1922.

Ninety per cent of the patients were admitted to medical services, only 4 were admitted to the urologic service. This is in accord with the fact that the causative lesion is usually in the heart. In 76.6 per cent of the 205 patients definite cardiac lesions were present. Furthermore, of 242 patients with bacterial endocarditis in the entire series of 14,411 autopsies, 55, or 22.7 per cent, had embolic infarction of the kidneys.

The causes of occlusion of the renal vessels are recorded in table 1.

Four of the five infants had thrombosis of a renal vein with infarction of an entire kidney. All four infants were emaciated and dehydrated incident to an acute infectious disease or malnutrition. Marshall and Whapham³ reported bilateral renal infarction in an infant, who died twenty days after the onset. No definite cause was found for the infarction.

TABLE 1—*Sources of Embolism or Thrombosis of the Renal Vessels*

	Cases
Rheumatic heart disease with	
Fibrillation and subacute bacterial endocarditis	3
Fibrillation without subacute bacterial endocarditis	27
Subacute bacterial endocarditis but no fibrillation	29
Neither fibrillation nor subacute bacterial endocarditis	1
Presence or absence of fibrillation not known	4
Coronary occlusion with mural thrombi	29
Coronary occlusion without mural thrombi	6
Sclerosis of aorta or renal arteries	24
Acute bacterial endocarditis	20
Pulmonary disease (empyema, infarcts, pneumonia)	7
Auricular fibrillation with intracardiac thrombi	7
Auricular fibrillation, no thrombi found	4
Hypertensive heart disease without auricular fibrillation	3
Intracardiac thrombi, cause not found	6
Syphilitic heart disease	1
Syphilitic aortitis with bacterial vegetations *	3
Venous thrombosis	4
Aneurysm of aorta	3
Septicemia and pyemia	3
Periarteritis nodosa	1
Not known	20

* These cases were reported by H. E. Martin and W. L. Adams Jr. (*Am Heart J* **16**: 714 [Dec.] 1938).

Seventy-three patients had only one renal infarct each. Two infarcts were present in each of 25 patients, and three or more in each of 105.

Bilateral infarction was found in 102 patients, infarction was present in the right kidney alone in 42 and in the left kidney alone in 56. These data seem to support the statement by Falcì⁴ that embolic occlusion is more frequent on the left side because the left renal artery forms an acute angle with the aorta.

No statement of the age of the infarcts was made in the records of 21 patients. The infarcts in 65 patients were classified as pale, those in 27, as both red and pale, those in 41, as red or recent, and those in 15, as both scars and recent infarcts. In 36 patients only scars were present in the kidneys. The frequency of healed infarcts (25 per cent) demonstrates that renal infarction does not necessarily indicate early death.

3 Marshall, S., and Whapham, E. Case of Bilateral Renal Infarction in Newly Born Infant, *Lancet* **2**: 428-429 (Aug. 22) 1936.

4 Falcì, E. Sur la necrose du rein, *J. d'urologie* **18**: 449-465 (Dec.) 1924.

The size of the infarcts was not stated in 69 records. They were less than 1 cm in diameter in 25 patients and between 1 and 2 cm in 55. Thirty were classified as large and 22 as small. One third of a kidney was infarcted in each of 3 patients, one half in 1 patient and an entire kidney or more in each of 9 patients.

Infarcts of other organs were present in 69 per cent of the patients. The spleen contained notable infarcts in 91 instances, the brain in 51 and the lungs in 50. Other organs were much less frequently involved.

In only 117 records was microscopic examination of the urine mentioned, and in most of these it was stated that only one specimen had been examined. The urine of 4 patients was grossly bloody. Thirty-five patients, or about 30 per cent of those whose urine was examined, had hematuria. (These 35 do not include any who had calculi, infection or tumors of the urinary tract.) Twenty-five of the 35 patients also had albuminuria. Albuminuria was recorded for 71 of the 133 patients whose urine was tested.

Sixty-seven per cent of the patients had some degree of fever, but in only 2 was the fever not explained by accompanying lesions. Both of these patients had infarction of an entire kidney or more, and the fever was of moderate degree.

The blood pressure was above 140 systolic and 90 diastolic in 34 per cent of the patients, but in no instance could it be proved that the rise was due to the renal infarction.

In 35 histories it was stated that abdominal or back pain had been inquired about, and in 14 this symptom was recorded as present. In 13 of the 14 patients either large or many small ones were present. The pain was recorded as being on the same side as a unilateral infarct in 3 cases, in 3 other cases it was present on one side and infarcts were found in both kidneys.

Of 44 histories in which tenderness in the costovertebral angle was mentioned, the sign was recorded as present in 14. In 11 of the 14 patients large or many small infarcts were found. In 2 patients the tenderness was on the same side as the unilateral infarcts and in 2 others tenderness on one side was associated with infarcts in both kidneys.

Six patients had nausea and vomiting, the degree of infarction was great in 5 of these.

In the histories of 9 patients mention was made of urinary symptoms not accounted for at autopsy by lesions other than renal infarcts. Nocturia and frequency of urination were each mentioned in 3 histories, dysuria in 2 and oliguria in 1.

Two patients had uremia. Both had extensive infarction of both kidneys.

REPORT OF CASE

At 6 p. m. on Jan. 14, 1938, an unmarried Mexican woman, aged 38, began to have pain in the middle of the back. It was aching in character at first, but within the next two hours it became severe and sharp and spread to the entire upper part of the abdomen. At the onset she had four shaking chills and felt feverish. She became very weak and dyspneic. The pain did not decrease in severity, and she passed no urine until the afternoon of January 16, at which time the pain lessened, and she began to void frequently, each time passing small amounts of bloody urine. There was no pain on urination.

During the three days between the onset of pain and her admission to the hospital she was nauseated and had vomited about twenty-five times—at first food and later clear fluid, but never blood

The patient had had three attacks of fever, with pain and swelling in the joints, at 6, 16 and 34 years of age. Moderate dyspnea on exertion and occasional palpitation had persisted since the initial attack. Edema of the ankles had been present for the past few years.

Examination—The patient appeared to be acutely ill. She was moderately dyspneic, and her lips and nails were cyanotic. She was perspiring, and her skin was cold. The veins of her neck were distended and pulsating. Her temperature was 96.8 F, pulse rate, 120, respirations, 40. The blood pressure was 96 systolic and 74 diastolic. The percussion note was normal over both lungs. There were bronchovesicular breath sounds and crepitant rales in the bases of both lungs posteriorly. The area of cardiac dullness was widened to the left. The apical rate was 174, the rhythm was absolutely irregular. The heart sounds were distant. The pulmonic second sound was accentuated. There was an apical systolic murmur. The abdomen was soft, distended and tympanic. There were tenderness in both costovertebral angles and generalized abdominal tenderness, maximum in the flanks and in the epigastrium. The tendon reflexes were normal. There was no edema.

The leukocyte count was 19,250 on admission.

Approximately 5 cc of bright red and almost clear urine was obtained by catheter. Benedict's test for sugar was negative. The urine showed coagulation and turned brown with Robert's reagent. Microscopic examination of the uncentrifuged urine showed red blood cells and leukocytes—one or two of each per high power field. When viewed under the spectroscope, the urine presented absorption bands characteristic of oxyhemoglobin.

The clinical impression on admission was rheumatic heart disease, with auricular fibrillation, and massive embolic infarction of the kidneys.

Course—Oxygen, warm blankets and morphine were used to counteract shock. Nine grains (0.58 Gm) of digitalis was given intravenously within twelve hours after admission. No more digitalis was given. On the morning after admission the blood pressure was 160 systolic and 106 diastolic. The heart rate was 140, the rhythm was more regular, with only short periods of fibrillation. The same afternoon the heart rate was 70 and the rhythm regular. The next morning the blood pressure was 146 systolic and 78 diastolic, the heart rate was 56 and regular. A loud systolic and a rumbling diastolic murmur were now heard over the area of the mitral valve.

During the forty-eight hours following admission the patient voided only four times, each time passing very small amounts of bright red urine. During the next two days she apparently had complete anuria.

From Jan 19 until her death on January 21, the patient gradually became irrational. The lungs became more edematous, and rapid changes occurred in the electrocardiogram, which suggested myocardial infarction (fig 1).

Postmortem Examination—Autopsy was performed one and one-half hours after death. The weight of the body was 170 pounds (77.1 Kg), the length, 64 inches (160 cm).

The heart weighed 400 Gm. The epicardium was covered by a very thin fibrinous exudate, and there were many tiny petechiae over the anterior surface of the apex. All the chambers except the left ventricle were dilated. There was a

smooth thrombus 2 cm in diameter in the left auricular appendage (fig 2) The thickness of the wall of the left ventricle was 12 mm, and that of the right ventricle was 5 mm The mitral leaflets were thickened and adherent and the chordae tendineae were shortened and greatly thickened The orifice of the mitral valve was of buttonhole appearance and was 6 cm in circumference The orifice of the aortic valve was also 6 cm in circumference, and the thickened leaflets were adherent at the commissures There were only a few atheromatous plaques in the aorta The pulmonary artery and its branches were thickened and arteriosclerotic

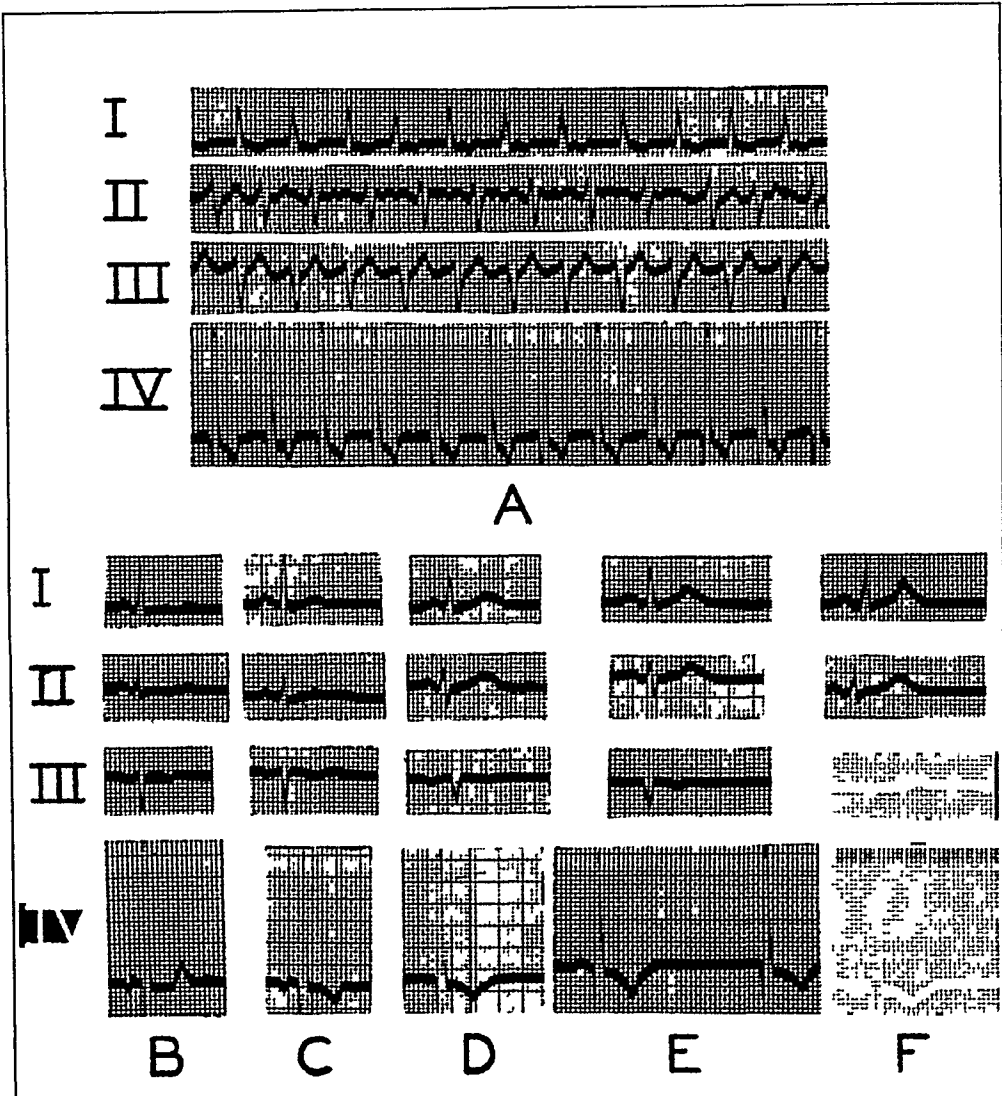


Fig 1—These tracings illustrate the rapid changes in the electrocardiograms of the case reported. Lead IV is the precordial lead with the electrode over the apex, the positive deflection being downward. The single complexes from B to F were cut to include exactly one cardiac cycle. A, 10 a m, Jan 18, a paroxysm of auricular fibrillation. B, 2 p m, Jan 18. C, about 9 a m, Jan 19. D, about 9 a m, Jan 20. E, 2 p m, Jan 20. Note sinus arrest with ventricular escape in lead IV. F, 9 a m, Jan 21, four hours before death.

The lungs, liver, gastrointestinal tract and spleen were normal except for moderate passive congestion.

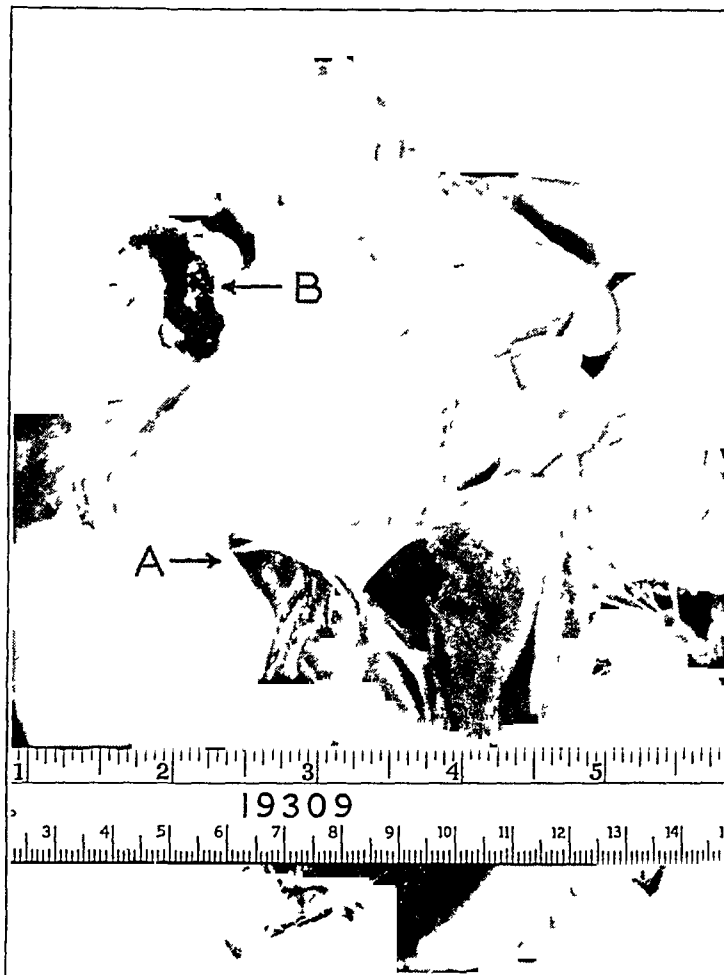


Fig 2—Posterior view of the opened left auricle and ventricle The mitral valve (*A*) is narrowed and the leaflets thickened The thrombus (*B*) can be seen in the left auricular appendage



Fig 3—Posterior view showing antemortem thrombotic material in both renal arteries The right kidney has been cut through the pelvis The dark areas are hemorrhagic and the pale areas necrotic tissue

The kidneys together weighed 400 Gm. The outer surfaces were mottled by large irregular hemorrhagic areas (fig 3). The normal markings at the cut surfaces were completely obliterated by large opaque pale areas and by irregular hemorrhagic zones. The renal arteries were both occluded through their entire lengths by loosely adherent antemortem thrombi. The bladder contained bloody urine.

The creatinine content of blood taken at autopsy was 14 mg per hundred cubic centimeters.



Fig 4—Photomicrograph of a section of one of the columns of Bertin. The small artery is thrombosed and the surrounding tissue is infiltrated with red blood cells and leukocytes. The cells of the tubules in this region are not completely necrotic. Hematoxylin and eosin stain, $\times 105$.

On microscopic examination, the heart and spleen appeared normal. The lungs showed minimal bronchopneumonia. In the kidney there was an area of reactive hyperemia below a narrow zone of partially necrotic tubules just under the capsule. Below the area of hyperemia all the tissue was necrotic, except for some viable tubules, filled with hyaline material, in the columns of Bertin. Many of the small veins and arteries were filled with thrombi (fig 4).

COMMENT

Complete simultaneous bilateral embolic occlusion of the renal arteries must be rare. There are several reports of oliguria, complete anuria and uremia due to extensive renal infarction,⁵ but we have not been able to find a report of a case similar to ours.

The changes in the electrocardiograms in the case which we have described resemble those observed by Master, Jaffe and Dack⁶ in a case of acute nephritis.

Hemoglobinuria following renal infarction has been mentioned by Danhez^{2e} and lately by Libman and Fishberg.⁷ Hemoglobin is liberated in the infarcted area by autolysis. In another case of early infarction of an entire kidney we have been able to demonstrate free hemoglobin in the involved kidney.

SUMMARY AND CONCLUSIONS

A case of complete simultaneous bilateral embolic occlusion of the renal arteries is reported in detail.

In a series of 205 cases of renal infarction the most common causes for occlusion of the renal vessels were bacterial endocarditis, auricular fibrillation with intra-auricular thrombi, coronary occlusion and arteriosclerosis.

Clinical symptoms and signs were frequently absent. When present they were usually associated with extensive infarction. In only 2 cases of the 205 in the series was the diagnosis made ante mortem. It thus appears that clinical diagnosis of this condition is to be based on

(a) Cardiovascular disease, this was noted in a little over four fifths of our material.

(b) Emboli in other organs, these were noted in two thirds of our cases.

(c) Severe pain in the back, tenderness in the costovertebral angle, urinary complaints, nausea and vomiting.

(d) Hematuria and impaired function of the affected kidney, in the absence of other reasonable causes.

The prognosis is usually that of the lesion causing the renal infarction.

5 (a) Lemierre, A., Laudat, M., and Laporte, A. *Étude de l'azotémie, de la chloremie et de la sécrétion urinaire dans un cas d'infarctus rénal. Remarques sur les indications et les effets de la cure de rechloruration*, Bull et mém Soc méd d hôp de Paris **48** 1224-1236 (July 18) 1932. (b) Lemierre^{2c}. (c) Folsom and Alexander^{2f}.

6 Master, A. M., Jaffe, H. L., and Dack, S. (a) *The Electrocardiogram in Acute Nephritis*, Am Heart J **12** 244 (Aug) 1936, (b) *The Heart in Acute Nephritis*, Arch Int Med **60** 1016-1027 (Dec) 1937.

7 Libman, E., and Fishberg, A. M. *Unilateral Hemoglobinuria. Its Occurrence in Infarction of the Kidney*, Ann Int Med **11** 1344-1347 (Jan) 1938.

DISTURBANCES OF RATE AND RHYTHM IN HYPERTENSIVE HEART DISEASE

NATHAN FLAXMAN, M D

Clinical Associate in Medicine, Loyola University Medical School
CHICAGO

The disturbances of rate and rhythm which occur in the course of hypertensive heart disease have been accorded little or no attention to date. Extrasystoles of the ventricular type are considered common, but no figures are available as to their frequency. Of other rhythmic disturbances, White¹ reported that in a group of 708 cases of hypertensive heart disease auricular fibrillation was noted in 92 (13 per cent), paroxysmal tachycardia in 11 (1.5 per cent), auricular flutter in 2 (0.3 per cent) and auriculoventricular block in 13 (1.8 per cent). The incidence of auricular fibrillation has been reported as 22,² 13,¹ 13.7³ and 25.3 per cent.⁴

Arrhythmias other than ventricular extrasystoles, such as auricular flutter, the various tachycardias, nodal rhythm and heart block, have been reported infrequently in series of cases of hypertensive heart disease, since they do not occur commonly in this condition. Nor are reports of individual cases common. Auricular flutter was noted as a result of hypertension in 12 (18.5 per cent) of 65 cases of flutter due to all causes.⁵ Isolated case reports of the various tachycardias have emphasized the arrhythmia and not the type of heart disease underlying the disturbance. Textbooks on heart disease make no mention of nodal rhythm or of heart block occurring solely on the basis of the effects of hypertension on the heart.

From the Department of Medicine, Loyola University School of Medicine

1 White, P. D. *Heart Disease*, New York, The Macmillan Company, 1934, p. 396.

2 Janeway, T. C. *A Clinical Study of Hypertensive Cardiovascular Disease*, *Arch. Int. Med.* **12**:755 (Dec.) 1913.

3 White, P. D. *A Note on the Common Occurrence of Serious Involvement of the Heart in Hypertension*, *New England J. Med.* **214**: 719, 1936.

4 Flaxman, N. *Auricular Fibrillation: Its Influence on the Course of Hypertensive Heart Disease*, *J. A. M. A.* **108**: 797 (March 6) 1937.

5 McMillan, T. M., and Bellet, S. *Auricular Flutter*, *Am. J. M. Sc.* **184**: 33, 1932.

In 1917 Musser ⁶ reported 2 cases of heart block associated with high blood pressure, aside from the work by Rosenthal,⁷ it is the only report of its kind in the literature to date. It is true that the disturbances of rate and rhythm probably occur with the same frequency in the common types of heart disease due to other causes, but they have certain characteristics in hypertensive heart disease which make them different.

ANALYSIS OF MATERIAL

An analysis of the arrhythmias found in 800 cases of uncomplicated hypertensive heart disease is presented in this report (table 1). All types included, the incidence of the arrhythmias was 30 per cent. The following irregularities were observed in 243 patients:

	No of Patients
Extrasystoles	28
Auricular	6
Nodal	7
Ventricular	15
Auricular fibrillation	198
Auricular flutter	3
Paroxysmal tachycardia	3
Auricular	1
Nodal	1
Ventricular	1
Nodal rhythm	4
Wandering pacemaker	1
Heart block	6

Prolongation of the PR interval (partial heart block), which was observed in 4 (0.5 per cent) of the 800 cases, will be considered in a subsequent article on the disturbances in conduction occurring in hypertensive heart disease. Bundle branch block has been reported on in detail in a previous publication.⁸

In the entire series of 800 patients, the ratio of men to women was 4:1. The same ratio applied to the 243 patients with the arrhythmias. An exception was the group of patients with extrasystoles, in which the ratio of men to women was 27:1.

The combined type of ventricular (congestive heart) failure occurred in 72 per cent of the total number of patients and in 70 per cent of those with arrhythmias, so that the type of hypertensive heart failure, as a rule, made little difference. The mortality in the two

⁶ Musser, J. H., Jr. Heart Block Associated with High Blood Pressure, *Arch Int Med* **20** 127 (July) 1917.

⁷ Rosenthal, S. R. Branch Arborization and Complete Heart Block, *Arch Int Med* **50**:730 (Nov) 1932.

⁸ Flaxman, N. The Course of Hypertensive Heart Disease. III. Significance of Bundle-Branch Block, *Ann Int Med* **11** 1607, 1938.

groups was about the same, 29 and 27 per cent, so that it was not the more seriously ill patients who had the arrhythmias

Extrasystoles—Extrasystoles occurred in 28 (3.5 per cent) of the total number of cases. They were ventricular in 13 cases (table 2), auricular and nodal in 4, nodal and ventricular in 2, auricular in 4 and nodal in 5 (table 3). Multiple extrasystoles were the rule rather than the exception. It has been said that the appearance of frequent

TABLE 1—*Analysis of Cases of Arrhythmia in 800 Cases of Hypertensive Heart Disease*

	Number of Cases	Incidence, Per Cent	Sex Ratio, M F	Ventricular Failure		Mortality, Per Cent
				Combined, Per Cent of Cases	Left, Per Cent of Cases	
Total series	800		4.1	72	27	29
Arrhythmias	243	30.4	4.1	70	30	27
Extrasystoles	28	3.5	27.1	67	33	35
Auricular fibrillation	198	24.8	4.1	70	30	25
Auricular flutter	3	0.4	3.0	100	0	33
Nodal rhythm	4	0.5	4.0	50	50	50
Paroxysmal tachycardia	3	0.4	2.1	66	33	33
Complete heart block	6	0.7	2.1	33	66	33
Wandering pacemaker	1	0.1	1.0	100	0	0

TABLE 2—*Multiple Ventricular Extrasystoles*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm	Heart Rate	Outcome
1	M	53	2 yr	Combined	20	90	Death, congestive heart failure
2	M	58	3 yr	Left	18	80	Regular rhythm
3	M	48	1 mo	Combined	18	90	Regular rhythm
4	M	63	2 wk	Combined	18	70	Regular rhythm
5	M	37	6 mo	Combined	23	80	Death, cerebral hemorrhage
6	M	45	1 yr	Combined	22	82	Regular rhythm
7	M	49	3 mo	Combined	20	92	Death, congestive heart failure
8	M	72	3 mo	Combined	18	86	Regular rhythm
9	M	71	6 mo	Combined	20	110	Death, congestive heart failure
10	M	72	2 yr	Left	22	100	Regular rhythm
11	M	65	6 mo	Combined	22	100	Regular rhythm
12	M	63	5 yr	Combined	22	100	Regular rhythm
13	M	69	2 wk	Combined	20	120	Regular rhythm

ventricular extrasystoles may be the forerunner of ventricular tachycardia, but this did not occur in my series. Only 2 of the 19 patients with premature ventricular beats had a bigeminal rhythm. No instances of trigeminal or quadrigeminal cycles were noted. The extrasystoles, except in the 2 cases of bigeminal rhythm, arose from multiple foci in the heart muscle. The immediate mortality, 35 per cent, was higher than in the entire series. Ten of the 28 patients with premature beats died while the arrhythmia was present. In 8 (80 per cent) of these 10 cases the cause of death was congestive heart failure; in 1 it was coronary occlusion, and in the other, a cerebral hemorrhage.

In only 3 of the 10 patients who died did the extrasystoles arise not only from multiple foci but also from several sources in the heart (auricle and ventricle in 2 and auriculoventricular node and ventricle in 1), so that this factor did not enter into consideration. The small difference in the mortality and the slightly higher number of deaths due to congestive heart failure in this group than in the entire series did not indicate that premature beats were of great clinical importance in the course of hypertensive heart disease. However, it should be kept in mind that they may be confused with auricular fibrillation, since they tend to be multifocal in origin.

TABLE 3—*Other Types of Extrasystoles*

Case	Sex	Age	Type of Beats	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm	Heart Rate	Outcome
1	M	49	Auricular and ventricular	2 mo	Combined	20	116	Death, congestive heart failure
2	M	65	Auricular and ventricular	3 yr	Left	23	80	Compensation
3	M	49	Auricular and ventricular	2 mo	Combined	20	116	Death, congestive heart failure
4	M	65	Auricular and ventricular	3 yr	Left	23	80	Compensation
5	F	33	Nodal and ventricular	2 wk	Combined	18	130	Compensation
6	M	75	Nodal and ventricular	5 yr	Left	15	110	Death, congestive heart failure
7	M	47	Auricular	1 wk	Left	18	90	Death, coronary thrombosis
8	M	68	Auricular	1 wk	Left	18	90	Compensation
9	M	74	Auricular	2 mo	Left	23	88	Compensation
10	M	68	Auricular	1 yr	Combined	20	100	Compensation
11	M	50	Nodal	1 yr	Left	18	100	Compensation
12	M	63	Nodal	6 wk	Combined	23	80	Compensation
13	M	56	Nodal	2 yr	Combined	17	80	Death, congestive heart failure
14	M	56	Nodal	5 yr	Combined	18	110	Compensation
15	M	70	Nodal	1 mo	Combined	18	110	Death, congestive heart failure

Auricular Fibrillation—In a previous study of the influence of auricular fibrillation on the course of hypertensive heart disease,⁴ the incidence was found to be 25.3 per cent. It was noted that the irregularity was not a late manifestation entirely, since it occurred with equal frequency in all groups of patients. The incidence of auricular fibrillation in the present series was approximately the same as in 198 (24.8 per cent) of the 800 patients. The ratio of men to women was again 4:1.

Auricular fibrillation definitely influenced the course of the disease in 54 patients (27.3 per cent) in whom the rapid irregularity preceded and precipitated the congestive heart failure, and in 10 (18.5 per cent) of whom it led to early death from this cause, within one month after the onset. When the auricular fibrillation occurred after congestive heart failure had been present from one month to several years, it had no

apparent influence on the course of the disease except in relation to the cause of death and the comparative absence of additional complications commonly appearing in hypertensive patients

The lowest mortality, 25 per cent, occurred in patients with auricular fibrillation, mainly because of the rarity of coronary thrombosis. The cause of 45 (81.8 per cent) of the 55 deaths (table 6) was congestive heart failure. Coronary thrombosis caused only 2 deaths among these

TABLE 4—*Ages of Patients at the Onset of Auricular Fibrillation*

Ages	Men	Women	Total	Per Cent
31 to 40	9	5	8	4.1
41 to 50	43	9	52	26.2
51 to 60	67	16	83	41.9
61 to 70	34	13	47	23.7
71 to 80	6	2	8	4.1
Totals	153	45	198	100.0

TABLE 5—*Ages of Patients with Auricular Fibrillation at Time of Death*

Ages	Men	Women	Total	Per Cent
31 to 40	0	2	2	3.6
41 to 50	6	1	7	12.7
51 to 60	24	6	30	54.6
61 to 70	10	2	12	21.8
71 to 80	2	2	4	7.3
Totals	42	13	55	100.0

TABLE 6—*Causes of Death of 55 Patients with Auricular Fibrillation*

Causes	Men	Women	Total	Per Cent
Congestive heart failure	33	12	45	81.8
Uremia	2	1	3	5.5
Cerebral hemorrhage	1	0	1	1.8
Coronary thrombosis	2	0	2	3.6
Miscellaneous	3	1	4	7.3
Totals	41	14	55	100.0

patients with auricular fibrillation. The antagonism between auricular fibrillation and coronary thrombosis is not clear, but it has been noted before by Levine⁹ and by Parkinson and Campbell¹⁰

Auricular Flutter—There were 3 patients with auricular flutter, 1 of whom died of congestive heart failure during the attack of the arrhythmia (table 7). The condition in the other 2 was converted to

⁹ Levine, S. A. Coronary Thrombosis, *Medicine* 8: 245, 1929

¹⁰ Parkinson, J., and Campbell, M. Paroxysmal Auricular Fibrillation, *Quart J Med* 23: 67, 1930

sinus rhythm by means of digitalis and quinidine, but the 65 year old man failed to respond

Nodal Rhythm.—There were 4 hypertensive patients with nodal rhythm (table 8) and 1 with a wandering pacemaker. The arrhythmias persisted, and 2 of the 5 patients died, 1 of congestive heart failure and the other of coronary occlusion. The heart rate was normal, from 66 to 100, in all 5 patients, and neither digitalis nor quinidine affected

TABLE 7—*Auricular Flutter*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm	Heart Rate	Outcome
1	M	59	3 yr	Combined	16	320 160	Condition converted to sinus rhythm
2	M	65	3 yr	Combined	22	300 100	Death, congestive heart failure
3	M	52	4 mo	Combined	18	300 150	Condition converted to sinus rhythm

TABLE 8—*Nodal Rhythm and Wandering Pacemaker*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm	Heart Rate	Outcome
Nodal Rhythm							
1	M	68	4 yr	Combined	20	70	Compensation
2	M	56	2 wk	Left	22	90	Compensation
3	M	62	1 yr	Combined	20	100	Death, coronary thrombosis
4	M	47	3 mo	Left	19	66	Death, congestive heart failure
Wandering Pacemaker							
1	M	38	8 mo	Combined	21	116	Compensation

TABLE 9—*Paroxysmal Tachycardia*

Case	Sex	Age	Type of Tachycardia	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm	Heart Rate	Outcome
1	F	43	Auricular	6 mo	Combined	18	190	Regular rhythm
2	M	42	Nodal	3 wk	Left	19	100	Death, uremia
3	M	67	Ventricular	4 mo	Combined	20	170	Regular rhythm

the nodal rhythm. In those who recovered compensation was effected by use of digitalis, but the rhythm remained governed by the auriculo-ventricular node. Vischer and Lowell¹¹ reported a case of auriculo-ventricular rhythm in a 46 year old man, with decompensation and symptoms of two years' duration, the blood pressure was 210 systolic and 130 diastolic and the cardiac rate 52, but death occurred three days after admission to the hospital.

¹¹ Vischer, C. V., and Lowell, L. L. Auriculoventricular Nodal Rhythm, *Ann Int Med* 5:1010, 1932.

Paroxysmal Tachycardia—Only 3 instances of paroxysmal tachycardia were noted among the 800 patients, an incidence of 0.4 per cent. The ventricular rates were 190, 100 and 170 for each of the three types: auricular, nodal and ventricular, respectively (table 9). Schwab¹² reported 3 cases of paroxysmal tachycardia, in the first 2 of which the patients had hypertensive heart disease. His second patient had a nodal rhythm and died of uremia. The second patient in my series, a 42 year old man with nodal tachycardia, also died of uremia. Both patients with paroxysmal tachycardia, 1 with the auricular and the

TABLE 10—*Complete Heart Block*

Case	Sex	Age	Duration of Symptoms	Ventricular Failure	Size of Heart, Cm	Heart Rate	Outcome
1	M	55	1 wk	Left	19	70-19	Death during attack of Adams-Stokes disease
2	F	65	6 yr	Left	18	64-32	Compensation
3	F	41	6 mo	Combined	19	70-35	Death, congestive heart failure
4	M	70	3 yr	Left	18	90-45	Compensation
5	M	77	6 wk	Left	20	84-42	Compensation
6	M	64	1 yr	Combined	23	90-45	Compensation

TABLE 11—*Heart Rate in 422 Cases of Hypertensive Heart Disease with Regular Rhythm*

	Normal Rate	Sinus Tachycardia	Sinus Bradycardia
Number of cases	191	222	9
Incidence	45.3%	52.6%	2.1%
Ratio, male:female	4.6:1	2.4:1	9:0
Congestive heart failure	60.7%	80.1%	55.5%
Mortality	20.3%	39.2%	22.2%
Average ventricular rate	61.99	100.150	50.60

other with the ventricular type, recovered with compensation after quinidine had corrected the marked rhythmic disturbance.

Heart Block—Six hypertensive patients had complete heart block, with ventricular rates between 19 and 45 beats per minute (table 10). Five of the 6 had a 2:1 block. The sixth patient, who had a 4:1 block, with a ventricular rate of 19 beats per minute, died during an attack of Adams-Stokes syndrome one week after the onset of isolated left ventricular failure. Another patient died of congestive heart failure six months after the heart failure and the complete block had appeared. The other patients were alive six weeks, one year, three years and six years, respectively, after the block became established.

12 Schwab, E. H. Observations on the Etiology and Treatment of Paroxysmal Ventricular Tachycardia, *Am Heart J* 6:404, 1931.

Association of Arrhythmias—No combination other than auricular fibrillation associated with bundle branch block was noted among the 243 patients with the arrhythmias. The absence of associated disturbances was probably due to the lack of acute physiologic and pathologic changes in the heart muscle or in its blood supply. This leads to the important consideration that once a permanent arrhythmia develops in the heart of a patient with hypertension other disturbances of rhythm do not appear, for instance, in patients with acute conditions of the coronary arteries,¹³ acute changes in the blood supply and in the heart muscle often lead to the occurrence of two or more arrhythmias simultaneously, in close association or in succession.

Normal Heart Rate—In 191 patients (45.3 per cent of 422 with regular sinus rhythm) the heart rate was between 61 and 99 beats per minute during the entire period of observation (table 11). Combined ventricular (congestive heart) failure occurred in 60.7 per cent of these patients. The mortality was 20.3 per cent. With the normal rate and rhythm and the lower incidence of combined ventricular failure, 23 (58.7 per cent) of the 39 deaths were due to congestive heart failure. However, a hypertensive patient in whom cardiac failure developed and whose heart rate remained regular and did not go above 99 beats per minute had a good chance to recover completely.

Sinus Tachycardia—The importance of tachycardia as a prognostic sign and as an index of hypertensive heart failure has not been mentioned heretofore. With the cardiac rate between 100 and 150, as it was in 222 (52.6 per cent) of the 422 patients with regular sinus rhythm, the incidence of combined ventricular (congestive heart) failure rose to 80.1 per cent and the mortality to 39.2 per cent. This was a 20 per cent increase, both in the incidence of congestive heart failure and in the mortality over the values for patients with a normal heart rate. The ratio of the causes of death in the two groups remained in proportion.

Simple Bradycardia—Exclusive of the cases of heart block, 9 men (2.1 per cent) had a persistent heart rate between 50 and 60 beats per minute. In 5 of these (55.5 per cent) congestive heart failure developed, and the mortality was 22.2 per cent. There was little difference as to the degree of failure and the mortality between those who had simple bradycardia and those who had a normal heart rate.

SYMPTOMS

Frequently the first definite indication of cardiac involvement was the appearance of an arrhythmia. In one fourth of the patients who had auricular fibrillation the arrhythmia was the first sign, and because

13 Master, A. M., Dack, S., and Jaffe, H. L. Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis, *Ann Int Med* **11** 735. 1937

of the rapid irregular rate, evidence of myocardial insufficiency appeared within a few days. Although multifocal ventricular extrasystoles, auricular flutter and paroxysmal tachycardia were not as common, it was true also of them. The rapid rate induced such symptoms as palpitation, breathlessness, weakness and occasionally precordial distress or even actual pain. Severe symptoms were generally noted with the sudden onset of rapid fibrillation, auricular flutter or paroxysmal tachycardia. The sudden onset and the appearance of the patient often gave the impression of acute coronary occlusion, but the quick improvement and the adaptation of the undamaged heart to the rapid ventricular rate usually disproved the original diagnosis.

At the other extreme were the effects of a slow ventricular rate, as in complete heart block, which occasionally manifests itself clinically by attacks of the Adams-Stokes syncope, convulsions and coma. This syndrome was an exceedingly rare occurrence during the course of hypertensive heart disease. It was noted only once among 6 cases of complete heart block in my series. One patient had no evidence of congestive heart failure, but died one week after the onset of the heart block, during an attack of the Adams-Stokes syndrome.

MECHANISM OF PRODUCTION OF ARRHYTHMIAS IN HYPERTENSIVE HEART DISEASE

It is difficult to explain the occurrence of arrhythmias in a heart which shows no involvement other than hypertrophy of the muscle fibers and dilatation of the organ itself. Of all the factors which seem necessary to initiate a cardiac arrhythmia, the important one here is impaired nutrition or altered metabolism of the heart muscles. The relation of anoxemia to the arrhythmias is not easy to determine. In evaluating the effects on the heart of acute thrombosis of the coronary arteries, it has been accepted as the mechanism behind the production of the arrhythmias. However, in cases of hypertension in which no evidence can be found in the heart of definite disturbances in the muscle or in the blood supply, this theory is seriously questioned. No doubt there are temporary deficiencies in nutrition of the heart and interference with the metabolic activities in order to bring about such marked disturbances in rate and rhythm.

The relationship between anoxemia and the cardiac irregularities was emphasized by Carter, Andrus and Dieuaide¹⁴. No marked changes in the coronary arteries are necessary in order to have anoxemia of the heart muscle. In hypertension the great increase in muscle mass, with

14 Carter, E. P., Andrus, E. C., and Dieuaide, F. R. A Consideration of the Cardiac Arrhythmias on the Basis of Local Circulatory Changes, *Arch. Int. Med.* **34** 669 (Nov.) 1924.

the demand for a greater capillary blood supply, is generally met and compensated for by enlargement of the heart. When the rate is normal there is difficulty only after many years. When the rate becomes rapid local anoxemia is more apt to occur and to induce arrhythmia. Anoxemia leads to the local accumulation of lactic acid, which interferes with the development of the excitatory process and its normal propagation. Thus there may be a local area in which diminished conductivity or spontaneous excitation may give rise to an ectopic rhythm. In particular, anoxemia may decrease the refractory period in the auricles, leading to the "circus movements" of auricular fibrillation and flutter.

The relationship of heart failure to arrhythmias, especially auricular fibrillation, has been discussed by Luten¹⁵. He stated that the tachycardia which occurs in heart failure is a compensatory mechanism and that auricular fibrillation usually is secondary to, and not the cause of, the heart failure. He expressed the belief that in the presence of auricular damage dilatation and stretching of the auricular wall from increased intra-auricular pressure associated with ventricular insufficiency is the predisposing factor in the production of auricular fibrillation. The same explanation could be applied to auricular flutter and auricular tachycardia. Vaquez¹⁶ and Nahum and Hoff¹⁷ also concluded that auricular distention is responsible for the frequent association of auricular fibrillation and heart failure.

Tachycardia often develops in the presence of a hypertrophic heart and usually brings on premature failure¹⁸. During diastole the left ventricle receives its blood supply, and an increase in heart rate interferes with the oxygenation of the heart muscle fibers. The tachycardia not only goads the weak muscle to more frequent contractions but deprives the harassed myocardium of adequate nourishment. The importance of this mechanism of heart failure in hypertensive heart disease, and not that of ventricular failure plus auricular distention, is substantiated. In over one fourth of patients with hypertensive heart disease the fibrillation preceded and precipitated the congestive heart failure. It was in such patients that the arrhythmia influenced the course of the disease. The fibrillation had no influence on the ultimate course of the disease.

15 Luten, D. The Relationship of Tachycardia to Cardiac Insufficiency, *Am Heart J* **12** 435, 1936. Luten, D., and Jeffreys, E. O. The Clinical Significance of Auricular Fibrillation, *J A M A* **107** 2099 (Dec 26) 1936.

16 Vaquez, H. Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924, p. 603.

17 Nahum, L. H., and Hoff, H. E. Auricular Fibrillation in Hyperthyroid Patients Produced by Acetyl- β -Methylcholine Chloride, with Observations on the Role of the Vagus and Some Exciting Agents in Genesis of Auricular Fibrillation, *J A M A* **105** 254 (July 27) 1935.

18 Murphy, F. D., Woods, R. M., and Grill, J. Hypertensive Heart Disease, *Minnesota Med* **20** 627, 1937.

among those in whom the congestive heart failure was present before the arrhythmia appeared. Also, in those with auricular flutter or with paroxysmal tachycardia the arrhythmia invariably preceded and precipitated the heart failure. Lastly, the fact that the rhythm remains regular in the majority of cases of hypertensive heart failure, even in some of the severest forms, speaks against the theory of auricular distention. Heart failure with dilatation of the auricle probably exerts little or no influence in the initiation of the arrhythmias in hypertensive heart disease. The irregularities are more prone to induce the myocardial insufficiency and precipitate the hypertensive failure.

PROGNOSIS

In general, hypertensive patients with a cardiac arrhythmia had a little better prognosis than those with regular rhythm, mainly because of the infrequency of coronary thrombosis. Exceptions were patients with multifocal extrasystoles and nodal rhythm. From the standpoint of incidence, auricular fibrillation was the most important arrhythmia. It had the lowest mortality, death occurring mainly among those in whom the irregularity preceded and precipitated the congestive heart failure. As to the other arrhythmias noted in table 1, the number of cases was too small to allow any general conclusions.

TREATMENT

Since the arrhythmias in hypertensive heart disease invariably indicate imminent failure of the hypertrophic heart or occur in the presence of insufficiency, and since they are usually permanent, specific treatment with digitalis is almost always necessary. The only other specific drug of value in the therapy is quinidine sulfate, which is especially useful in cases in which auricular fibrillation is the first sign of cardiac involvement. In the absence of congestive heart failure quinidine sulfate is the drug of choice for the treatment of the common arrhythmias.

With the exception of those with the auricular and ventricular types of paroxysmal tachycardia, digitalis is given to all patients with hypertensive heart failure, regardless of whether it is the common combined ventricular type, the less common isolated left ventricular type or the uncommon isolated right ventricular type. Rest in bed is advised and morphine given, depending on the severity of the symptoms associated with the heart failure. Sedatives were used extensively for all the patients in this series, regardless of the fact that many were ambulatory during the treatment for the arrhythmia.

SUMMARY

The study of 243 cases of arrhythmia among 800 cases of hypertensive heart disease, an incidence of 30 per cent, is reported.

The most common arrhythmia was auricular fibrillation, it occurred in 198 (81.5 per cent) of the 243 patients. It had the best prognosis except in cases in which the fibrillation preceded and precipitated congestive heart failure.

Arrhythmia may occur at any time during the course of hypertensive heart disease and often is the first indication of cardiac involvement. It does not tend to show spontaneous remission, to change in character or to become associated with or followed by another type of arrhythmia.

The mortality among patients with arrhythmias was lower than among those with regular sinus rhythm, owing to the comparative absence of coronary thrombosis. Seventy-five per cent of the patients with auricular fibrillation, 66 per cent of those with auricular flutter, paroxysmal tachycardia or complete heart block, 65 per cent of those with extrasystoles and 50 per cent of those with nodal rhythm survived, some of them for a considerable number of years.

The cardiac rate was important as a prognostic sign because the mortality among those with a regular rate above 100 beats per minute was 39.2 per cent, while those with a regular normal rate had a mortality of 20.3 per cent. Of the patients with sinus tachycardia, 80 per cent had combined ventricular (congestive heart) failure, as compared with only 60 per cent of those who had a normal sinus rate and rhythm.

Since the arrhythmia often led to myocardial insufficiency, if this was not evident already, and tended to be permanent, treatment with digitalis or quinidine sulfate was necessary. Digitalis was indicated when the symptoms or signs or both of congestive heart failure were present regardless of the arrhythmia (with the exception of auricular or ventricular types of paroxysmal tachycardia). Quinidine was indicated especially for the treatment of auricular fibrillation or paroxysmal tachycardia in the absence of signs of congestive heart failure.

CLINICAL CHARACTERIZATION OF PRIMARY CARCINOMA OF THE BODY AND TAIL OF THE PANCREAS

HYMAN LEVY, M D

AND

S S LICHTMAN, M D

NEW YORK

Carcinoma of the body and tail of the pancreas is by no means a rarity, yet its diagnosis is felt to be difficult because physical findings are commonly absent and the symptom complex is vague in many of the cases

The clinical characteristics of primary neoplasm of the head of the pancreas have been recognized since Dieulafoy¹ described jaundice due to obstruction of the common bile duct. In 1908 Chauffard² differentiated between the cancer involving the head of the pancreas, termed *pancreatico-biliaire*, and that involving the body and tail, designated *pancreatico-solaire*. The latter characterization was based on the supposed localization of the pain in the region of the solar plexus, as a result of invasion by the pancreatic tumor. This type of pain, however, is observed only in isolated instances.

Several observers have described a definite mental pattern of anxiety, nervousness, depression and insomnia in patients suffering from carcinoma of the pancreas³. Some of these patients have been labeled as psychoneurotic, yet, despite the absence of objective findings, the pain has been so constant as to arouse suspicion of a definite organic lesion⁴.

Between the years 1926 and 1935, inclusive, the opportunity was afforded us to observe 19 patients with carcinoma of the body and tail of the pancreas. We have analyzed our observations in an endeavor to formulate more satisfactory diagnostic criteria.

From the Medical Division, the Mount Sinai Hospital, service of Dr. George Baehr.

1 Dieulafoy, G. Manuel de pathologie interne, ed 15, Paris, Masson & Cie, 1908, vol 2, p 1038.

2 Chauffard, M. A. Le cancer du corps du pancreas, Bull Acad de med, Paris 60 242, 1908.

3 (a) Yaskin, J. C. Nervous Symptoms as Earliest Manifestations of Carcinoma of the Pancreas, J A M A 96 1664 (May 16) 1931. (b) Latter, K. A., and Wilbur, D. L. Psychic and Neurologic Manifestations of Carcinoma of the Pancreas, Proc Staff Meet, Mayo Clin 12 457, 1937.

4 Bourne, G. Pain as the Only Sign of Pancreatic Carcinoma, Lancet 2 1326, 1936.

ANALYSIS OF PHYSICAL FINDINGS

One hundred and twenty-two cases of primary malignant neoplasm of the pancreas, in which the diagnosis was confirmed by laparotomy or necropsy, have been studied. From among these, 19 cases in which the neoplasm involved primarily the body and tail of the pancreas have been selected as suitable for study.^{4a} The clinical data are summarized in table 1.

TABLE 1—*Clinical Data*

Case	Sex	Age, Yr	Duration of Symptoms, Mo	Presenting Symptom at Onset	Gastrointestinal Symptoms		Diabetes, Duration	Loss of Weight	
					Anorexia	Vomiting		Lb	Mo
1	F	50	1	Ascites, edema of legs	+	0	9 mo	40	18
2	M	47	5	Abdominal pain	+	0		40	2
3	M	47	4	Epigastric pain	+	0	17 yr	16	4
4	M	49	6	Epigastric pain	+	0		36	5
5	M	69	2	Lumbar pain	+	0		21	2
6	F	55	3	Asthenia	+	0	8 yr	15	3
7	M	60	3	Epigastric pain	+	0		20	3
8	M	42	1½	Pain in left lower quadrant of abdomen and lumbar pain	+	0		20	2
9	M	65	2	Swelling of left lower extremity	+	0			
10	F	59	3	Abdominal pain	+	0		26	24
11	M	52	1½	Lower posterior thoracic pain	+	0		15	2
12	F	56	5	Pain in left lower quadrant	+	0		33	5
13	F	47	37	Anorexia, pain in left thigh	0	0			
14	M	69	½	Pain in left upper quadrant of abdomen	+	+	2 wk	70	48
15	M	37	5	Umbilical pain	+	0		28	4
16	M	24	12	Epigastric pain	+	0		20	24
17	M	50	1	Lumbar pain	+	0		20	1
18	M	53	5	Abdominal pain	+	0			
19	F	53	30	Epigastric pain, vomiting	+	+		50	30

4a These 19 cases, in which only the body and tail of the pancreas were involved, comprise 15 per cent of the 122 cases of pancreatic carcinoma. This incidence may be compared with the percentages reported by others: 46, by Hick and Mortimer,⁵ 32, by Eusterman and Wilbur,⁶ and 33, by Riese.⁷ The lower incidence in our series probably is a result of a stricter selection of cases, which eliminated, as a rule, those in which the head of the pancreas was also involved. Isolated instances in which the involvement of the head of the pancreas was terminal have been included.

5 Hick, F K, and Mortimer, H M. Carcinoma of the Pancreas, *J Lab & Clin Med* **19** 1058, 1934.

6 Eusterman, G B, and Wilbur, D L. Primary Malignant Neoplasm of the Pancreas. Clinical Study of Eighty-Eight Verified Cases Without Jaundice, *South M J* **26** 875, 1933.

7 Riese, H. Die Chirurgie des Pankreas, in Kirschner, M, and Nordmann, O. Die Chirurgie, Berlin, Urban & Schwarzenberg, 1927.

Age and Sex—There were 12 male and 7 female patients in the series. There was 1 man in the third and 1 in the fourth decade of life, 4 men and 1 woman in the fifth, 4 men and 4 women in the sixth, and 2 men and 2 women in the seventh. Of the 7 patients under 50 years, all but 1 were males.

Duration of Symptoms—Symptoms were present for from three weeks to approximately a year before hospitalization. Two patients with malignant degeneration of pancreatic cysts had symptoms of longer duration—two and one-half and three years, respectively.

Mode of Onset—In 15 of the 19 patients the presenting symptom was some type of pain. In the remaining 4 the initial symptoms were, respectively, anorexia, asthenia, ascites and swelling of the lower extremities.

Weight Loss—For 15 patients loss of weight was accurately recorded, nine of these lost weight over a period of four months or less, the loss ranged between 15 and 40 pounds (7 and 18 Kg) and averaged 21.5 pounds (9.5 Kg). The remaining 6 patients lost weight over a period of four to thirty months, the loss ranged between 20 and 50 pounds (9 and 22.5 Kg) and averaged 34 pounds (15.5 Kg).

Distribution of Pain—Of the 18 patients who exhibited pain at some time during their clinical course, 13 had abdominal pain. This pain was diffuse in 3, in 6 it was restricted to the epigastrium, in 2 to the left upper quadrant, in 1 to the left lower quadrant and in 2 to the umbilicus.

Lumbar pain occurred in 4 patients. It was bilateral in 1, on the left side in 2 and on the right side in the fourth. There was radiation of the pain to both inguinal regions in 1 patient and to the outer aspect of the thigh in 2 patients.

In the remaining patient, an unusual distribution of pain was noted, encircling the left lower portion of the chest, from the lower thoracic spine around the left side of the hypochondrium to the xiphoid process.

Gastrointestinal Symptoms—Marked anorexia occurred in all but a single patient. Vomiting occurred in but 2 patients. Diarrhea did not occur, constipation was noted in several patients.

Cough—Of 4 patients who exhibited cough as a symptom, in 2 it could be attributed definitely to neoplastic invasion of the lung and mediastinum. In a third patient the cough was conditioned by associated bronchiectasis.

Ascites—In 6 patients ascites developed. It was hemorrhagic in 4, in 2 it was the result of diffuse peritoneal metastases. In 2 patients it was the result of direct extension of the neoplasm into the portal vein. In 2 of the patients there was swelling of the lower extremities, in the first it resulted from thrombosis of the left common iliac vein, and in the second it was probably secondary to the ascites.

Associated Diabetes Mellitus—Impaired carbohydrate metabolism was noted in 5 patients. Diabetes mellitus had existed in 2 patients for seventeen and eight years, respectively. In a third patient known diabetes had preceded the onset of the new symptoms by only nine months. In the remaining 2 patients, disturbed carbohydrate metabolism became manifest by hyperglycemia or decreased tolerance as shown by the dextrose tolerance test or both.

Venous Thromboses—Six patients exhibited venous thromboses resulting mainly from direct neoplastic compression or extension. In 1 patient the portal and splenic veins were involved. In 2, the splenic vein alone, in another, mediastinal metastases had compressed the superior vena cava, with resulting thrombosis of this structure. In the remaining 2 patients the thrombosis occurred in the left common iliac and in the left femoral vein respectively.

Palpable Mass—In 9 of the 19 patients a definite *epigastric* mass was palpable at the time of admission. In 2 others this finding was equivocal. In the remaining 8 patients palpation did not reveal any masses.

Enlargement of Liver and Spleen—In 13 patients the liver was enlarged to various degrees, as determined either by exploration or at postmortem examination. In practically every instance the enlargement was directly associated with diffuse hepatic metastases.

The spleen was enlarged in 3 patients. The greatest enlargement was the result of carcinomatous invasion and obliteration of the portal vein. In another patient the splenic vein was obliterated through compression by the tumor. In the third patient, the spleen was only slightly enlarged as a result of metastases within it.

ANALYSIS OF LABORATORY FINDINGS

Hemoglobin Estimations—The hemoglobin content of the blood was determined in 18 of the 19 cases. In 16 the hemoglobin content was above 70 per cent, in 7 it ranged between 80 and 90 per cent, in 4, between 90 and 100 and in the remaining 5 between 70 and 80.

In the two instances in which the hemoglobin content fell below 70 per cent, it was 67 and 48 per cent, respectively. The latter low level occurred in the youngest member of the group, who had been ill for one year and in whom widespread metastases had been present for many months.

Leukocytosis—In 11 of 18 cases the leukocyte count was 10,000 or more (10,400 to 28,800), and the percentage of polymorphonuclear cells ranged between 66 and 92. In 2 of the remaining 7 cases the leukocyte count was less than 6,000.

Icterus Index—In 7 of the 9 instances in which the icterus index was determined it was normal.

Cholesterol Partition—Cholesterol of the blood was determined in 8 cases, and in 7 the value was normal. In a single instance hypercholesteremia (340 mg per hundred cubic centimeters) was present (case 11, table 2). In 5 instances the cholesterol ester fraction was determined and was found normal except in 1 instance (case 5), in which the ester fraction decreased to a mere trace.

Blood Amylase—In 5 cases blood amylase was determined by the method of Elman⁸. In 3 it was at the lower limits of normal. In only 1 instance (case 11) was it increased—to 175 and to 15 units.

Blood Sugar—Estimations of blood sugar were made in 11 instances. In 6 a normal level was found. Hyperglycemia (145 to 395 mg of sugar per hundred cubic centimeters) was noted in the remaining cases. In 3 instances dextrose tolerance was tested. A sugar tolerance curve of the diabetic type was obtained in 2 cases (10 and 11).

Occult Blood in Stool—The guaiac test for occult blood in the stool was made in 11 cases. In only 2 did the test prove positive.

Roentgen Findings—In 9 cases the gastrointestinal tract was studied after a barium sulfate meal. In 3, the findings were negative. Of the remaining 6 cases, in 3 the examination showed gastric and prepyloric defects and in 3 duodenal distortion or defect.

8 Elman, R., Arneson, N., and Graham, E. A. Value of Blood Amylase Estimations in Diagnosis of Pancreatic Disease, *Arch Surg* 19 943 (Dec) 1929.

TABLE 2—Laboratory Data

Case	Hemoglobin, %	Leukocytes, Thousand	Polymorphonuclear Neutrophils, %	Icterus Index	Van den Bergh Reaction	Cholesterol / Cholesterol Esters, Mgr per 100 Cc	Bilirubinemia, Mgr per 100 Cc	Blood Amylase, Units	Gastric Acidity	Occult Blood in Stool	Pancreatic Ferments	Blood Sugar, Mgr per 100 Cc	Roentgen Findings	Special Pathologic Changes
1	80	12.2	86		Dir neg		0.7			0		330		Stenosis of portal vein
2	72	24.0	88		Ind 1/125,000	150	0.8			0				Hemorrhagic peritoneal fluid
3	85	6.0	56	9	Dir neg	230/70	0.2	1.8	14/34	0	Trypsin neg diastase 80	215	Gastrointestinal tract normal	
4	98	7.7	70		Ind 1/500,000				40/50	0			Incomplete duodenal obstruction	
5	87	7.0	58	7	Dir neg	205/trace	0.2	1.3		0		120	Gastrointestinal tract 1 posterior wall lesion? 2 normal	
6	70	13.0	87		Ind 1/500,000					0		395	P eural effusion	Pulmonary embolic thrombosis of splenic vein
7												106	Prepyloric distortion	
8	85	9.0	73		Dir neg		0.3		16/40	—		104	Gastrointestinal tract normal, barium sulfate enema neg	Infiltration of stomach, spleen, adrenals, liver and hepatic duct
9	75	15.5	92			280			36/42	—		115		Thrombosis of left common iliac vein and vena cava, invasion of left adrenal and left ureter
10	81	10.4	66	25			0.9		/44	0		235	Duodenum dilated, antiperistalsis	Compression of portal vein, obliteration of splenic vein, left hydro nephrosis
11	82	6.3	76	60 (late)	Dir pos on later admission	340/170	2.5 (late)	17.5	22/12	—	Trypsin neg diastase trace	85	Gastrointestinal tract normal, gallbladder faintly visualized	
12	67	5.3	52	7	Dir neg		0.2		0/20	0			Prepyloric defect	
13	92	14.0	78	7	Dir neg	225/70	0.2			—		350		Hemorrhagic peritoneal fluid
14	100	21.5	92							—				Hemorrhagic peritoneal fluid, carcinomatous thrombosis of splenic and portal veins
15	98	13.0	79	8	Dir neg		0.3	1.8	64/56	+			Gastrointestinal tract filling defect of duodenum, with retention, gallbladder failure of visualization	
16	48	5.4	75		Dir neg		0.2			—		75	Widespread bony metastases	Peripancratic abscess, hepatic abscess, subdiaphragmatic abscess
17	78	28.8	88	12	Dir neg	180/37	0.2			—			Flat plate of abdomen negative	Metastases to upper lobe of right lung
18	82	12.7	76							0			Pulmonary metastases	Thrombosis sup vena cava
19	75	15.0	64	9		160		6.4		Trace		85	Enlarged mediastinal glands	Thrombosis of left femoral vein, embolus to branch of right pulmonary artery
								1.0				125		

RÉSUMÉ OF SIGNIFICANT FINDINGS

A review of the more important findings in the analysis of our material indicates that carcinoma of the body and tail of the pancreas occurred in a significant percentage of cases of carcinoma of the pancreas in men under 50 years of age. The outstanding symptoms were pain of various types, rapid loss of weight, marked loss of appetite and a tendency, in some patients, to a disturbance in carbohydrate metabolism similar to diabetes mellitus. In half of the patients a definite abdominal mass was palpable. In the majority of the patients there was hepatic enlargement and in a few splenic enlargement. In over half the patients either ascites or venous thromboses occurred. Anemia was remarkable by its absence. Roentgen examination of the gastrointestinal tract gave material diagnostic aid in the majority of the instances in which it was employed, gastric and duodenal distortion and defects were often demonstrable.

COMMENT

Disease of the body and tail of the pancreas provides a great diagnostic problem. Buried deep in the abdomen and provided with a narrow duct through which a colorless secretion drains into the bowel, the pancreas challenges the scrutiny of the physician.

In about one sixth of the cases neoplastic disease of the pancreas involves the body and tail alone. Because of the frequency of secondary or terminal invasion of the head it is likely that among cases of the disease in the earlier stages the percentage of cases in which the body and tail alone are involved is greater. Victims of the disease under the age of 50 are predominantly males.

Symptoms may be present for as long as one year before medical advice is sought by the patient, and when the malignant change supervenes on a pancreatic cyst the interval may extend to as long as three years.

Appreciable losses of weight (averaging 27 pounds) are characteristic. So constant and striking has this finding been, that when the symptom is observed in the absence of other diseases that regularly produce loss of weight, such as diabetes, hyperthyroidism, tuberculosis, anorexia nervosa, sprue or demonstrable malignant growth, one should suspect and attempt to exclude tumor of the pancreas.

Pain—Because of the paucity of objective physical and laboratory findings in the disease, pain, which was present in 90 per cent of our patients, is a particularly important symptom. A great variety of types of pain may occur, hence mistaken diagnoses of spondylitis, sciatic syndrome, intercostal neuralgia, renal calculus or diaphragmatic pleurisy may be made. Pain was the presenting symptom in 80 per cent of our

patients and in 44 per cent of the patients studied by Mussey⁹ It was the only symptom in a case reported by Bourne⁴ There are two main components to the abdominal pain, an anterior upper abdominal and a posterior lumbar radiation Eusterman and Wilbur⁶ studied the radiation of pain in 62 patients with malignant tumor of the pancreas and found that in one third of them the pain radiated to the back either directly or around the costal margins In another one third of the patients the pain did not radiate In 9 patients the pain radiated to the upper quadrants of the abdomen, to the left in 4 and to the right in 5 A rare but interesting radiation is toward one or the other thigh Hick and Mortimer⁵ reported a case in which the tumor tissue had invaded both ureters, from retroperitoneal metastases, thus producing hematuria and pain radiating to the groins One patient in our series presented a similar type of radiation of pain, and necropsy revealed that the ureter was invaded by the tumor

When the pain radiates toward the right side it may simulate that of gallbladder disease When it is persistently epigastric and radiates through to the back it simulates that of a penetrating lesion of the stomach, either an ulcer or a carcinoma, frequently, however, the pain is unrelated to events of the digestive cycle It often extends bandlike around the left side as a girdle zone, involving a somatic area innervated by the eighth to eleventh dorsal nerves, and simulates the segmental pain of radiculitis and spondylitis¹⁰ (case 11) Katsch¹¹ reproduced pain typical of pancreatic disease by instilling 2 to 4 cc of ether into the duodenum The weight of the food-filled stomach pressing against the celiac plexus in some cases further increases the irritation of this structure and elicits pain Similarly, lying supine or leaning backward produces pressure which causes deep-seated epigastric pain extending to the back and radiating as if along the course of a lower intercostal nerve The initial left-sided pain is probably conditioned by implication of the splenic nerve and its branches, when the entire solar plexus is invaded the pain takes the typical location, median, transverse and supraumbilical

Latter and Wilbur^{3b} recently characterized the pain as more closely resembling that of lesions of the nervous system, such as root pain, than that of visceral disease

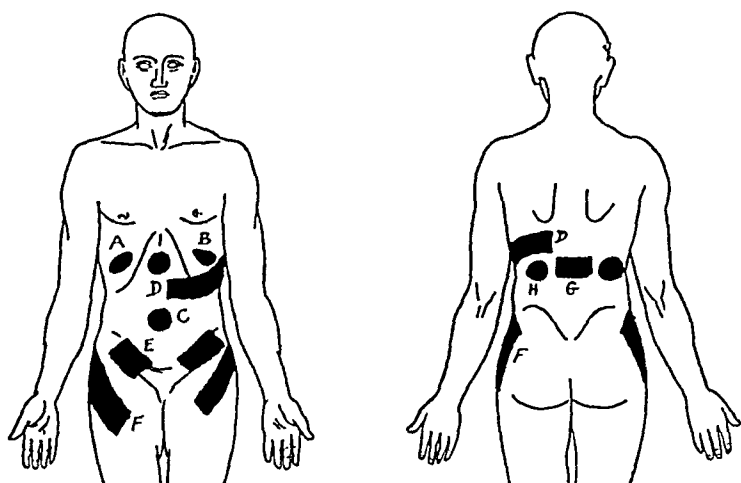
Chauffard referred to pains, simulating "gastric crises," of bulbo-spinal origin and also a "pseudo-aneurysmal" type He also pointed out

9 Mussey, R D Pancreatic Carcinoma, *M Clin North America* 3 681, 1919

10 Katsch, G Krankheiten der Bauchspeicheldrüse, in *Lehrbuch der inneren Medizin*, ed 3, Berlin, Julius Springer, 1936, p 926

11 Katsch, G, and von Friedrich, L Bauchspeichelfluss auf Atherreiz, *Klin Wchnschr* 1:112, 1922

a most significant characteristic of many patients with pancreatic malignancy—namely, the classic positions which they assume to obtain relief, sitting up, leaning forward in bed, or walking with the body leaning or bending forward at the hips, or lying curled up on the right side. One patient (case 10) assumed the prone position in order to obtain relief. Lying in bed in the usual recumbent position intensifies the pain. Indeed, occasionally the pain makes its first appearance at night, since lying supine places the nervous structures in front of the vertebral column, especially the solar plexus, under tension. Many carcinomas, such as those of the stomach, liver and lung, which metastasize to the retroperitoneal tissues produce pain in the back as a distressing symptom even in the absence of gross metastases to the spine, yet one does not observe postural relief of pain in these instances.



Areas of pain associated with neoplasm of the body and tail of the pancreas 1, epigastric or solar A, B, radiation to the upper quadrants of the abdomen C, umbilical D, intercostal, radicular, head zone E, groin, radiation from renal zone F, thigh, radiation from renal zone G, lumbar H, loin

We recall vividly a patient with pancreatic neoplasm who, suffering from persistent epigastric pain, was driven from his bed by the pain and sought relief by walking the hospital corridor. Partial or complete relief from pain by change of posture is a significant feature of the disease. The paroxysmal nature of the pain and the lack of relation to the digestive cycle characterize it further.

The areas in which pain occurred in our patients are represented in the figure. In 13 patients abdominal pain was localized in the epigastrium, the upper portion of the abdomen or the umbilical region. In 5 patients lumbar or loin pain, with or without radiation toward the inguinal region or thigh, was found. Such radiations are apparently conditioned by tissue invasion toward one or the other kidney, in one case the ureter was invaded, with resulting compression and hydronephrosis on the

affected side. While this type of radiation of pain was not the sole symptom in any of our cases, its occurrence was sufficiently frequent to be worthy of stress. The pancreaticorenal types of pain represent regional pain as well as the referred segmental pain of the kidney and pancreas. The inguinal and the thigh pains represent pains referred along the second lumbar segment.

Analysis of the pancreaticorenal types of pain and lesions in the kidney or ureter (table 3) shows no true correlation. However, in 5 of the 19 patients some form of renal pain was present, at times closely simulating that of renal calculous disease.

Abdominal Mass—Palpation of the tumor is difficult because of the inaccessibility of the pancreas. Examination with the patient in a tub of warm water may facilitate abdominal relaxation and permit palpation. A tumor was palpable in 45 per cent of our patients and in 69 per cent

TABLE 3—*Anatomic Findings Associated with the Pancreaticorenal Type of Pain*

Case	Distribution of Pain	Anatomic Changes
10	Bilateral anterior abdominal pain, radiating from nipples to iliac crests	Cancerous invasion of left ureter, left hydronephrosis
5	Bilateral lumbar pain radiating first to left and then to right inguinal region	(Exploratory operation done elsewhere)
8	Pain in left lumbar area and in left lower quadrant of abdomen, radiating to outer left thigh	Metastatic nodules in left kidney
17	Right lumbar pain radiating to right thigh and knee	No intrarenal or ureteral involvement, subdiaphragmatic abscess
13	Pain in left lumbar area and in lateral aspect of left thigh	Malignant degeneration of huge pancreatic cyst

of Eusterman and Wilbur's⁶. The gallbladder is more frequently involved in patients with icterus. In our series an epigastric mass was palpable in 50 per cent of the patients. Enlargement of the liver was present in two thirds of the patients. The spleen was palpable in 3

A tumor in the body of the pancreas is not fixed until quite late (Eusterman and Wilbur) and therefore may descend several centimeters on deep inspiration.

Gastrointestinal Symptoms—With a single exception, all of our patients suffered from anorexia, which was also a major complaint in 48 per cent of the patients in the series of Hick and Mortimer.⁵ According to Raymond,¹² the appetite may remain good despite marked loss of weight in some patients. Two of our patients had vomiting as a symptom.

Diarrhea was infrequent in patients of this series and of those reported by Eusterman and Wilbur⁶ and Hick and Mortimer. It occurs

12 Raymond, L. Cancer du corps du pancreas, *Presse méd* 37 627, 1929

more frequently when carcinoma of the head of the pancreas has completely occluded the pancreatic and common bile ducts Bourne⁴ found an increase in the percentage of neutral fat in the stools in a few cases

Occult blood was found in the stools of 2 of 11 patients In these 2 patients the neoplasm had invaded the stomach and duodenum In the absence of such invasion no occult blood was found in the stool This contrasts with the almost constant presence of occult blood in the stools of patients with gastric carcinoma In the series of Hick and Mortimer the stomach was involved by direct extension of carcinoma of the tail of the pancreas in 6 patients and the duodenum was invaded in 7, the frequent occurrence of blood in the stools is thus explained The duodenum was involved, to the extent of producing some degree of obstruction, in 10 patients in Eusterman and Wilbur's series of 88

Metastases—Metastases must be distinguished from direct extension of the primary pancreatic tumor Metastases to the lymph nodes in the upper region of the abdomen and to the liver occur most frequently, lymphatic spread to the mediastinal glands and to the pleura also occurs quite frequently Carcinomatous lymphangitis of the lung has been recorded In 4 of our patients neoplastic invasion of the lung and mediastinum occurred, in 1 patient it resulted in thrombosis of the superior vena cava and cough Hematogenous metastases occur rarely, in these rare cases lymphatic extension also occurs⁴ Hick and Mortimer recorded 1 case of carcinoma of the pancreas with metastasis to the umbilicus Hemorrhagic ascites developed in 2 patients as a result of diffuse peritoneal metastases

Carbohydrate Metabolism—Although hyperglycemia or frank diabetes mellitus occurs only infrequently in this disease, there is a tendency toward decreased carbohydrate tolerance, expressed, when a dextrose tolerance test is given, in a high or delayed dextrose curve In our own series there were 5 patients with diabetes preexisting to or coexistent with pancreatic tumor In 1 patient the duration of diabetes was seventeen years, in another, eight years In a third patient diabetes antedated the other symptoms by nine months, and in a fourth, by two weeks In a fifth patient there was no preceding history of diabetes, but at the time of admission the blood sugar was found to be 235 mg per hundred cubic centimeters Of these 5 patients, in 3 the diabetes was related to the pancreatic disease, the incidence of coexisting diabetes in the series was thus 15 per cent This is higher than the usual incidence (5 to 8 per cent) encountered in routine hospital practice in the same age group Dextrose tolerance tests have hitherto been performed infrequently on patients with pancreatic malignancy It is interesting to note that in 1 patient (case 11) the blood sugar during fasting

was 85 mg, yet the dextrose tolerance test showed a curve with a high plateau, the blood sugar rising to 300 mg at the second hour and remaining at 280 mg at the end of the third hour. This finding, together with elevated values for amylase, gave a clue to the underlying disease. Blood sugar during fasting was elevated (145 to 395 mg) in 5 of 14 patients whose blood sugar was estimated. The blood sugar values of the remaining nondiabetic patients in the group ranged from 65 to 145 mg. In the series of cases reported by Eusterman and Wilbur, glycosuria was infrequent, they encountered 1 case of hypoglycemia (blood sugar 40 mg). In the group reported by Hick and Mortimer there were 8 cases of diabetes, in 3 of which there was carcinoma of the body of the pancreas.

The disturbance in carbohydrate metabolism in our patients differed in several respects from that found in patients with primary diabetes mellitus. It could not be controlled readily by diet or insulin. Occasionally there was an unexplained spontaneous remission of the glycosuria, unrelated to diet or insulin. The fluctuating dextrose tolerance suggested that variations in circulatory and pancreatic duct pressure, rather than tumor invasion, were probably responsible for the glycosuria.

Central Nervous System—Yaskin^{8a} drew attention to the frequency of neurotic and psychic symptoms in patients with pancreatic malignancy. Recently Latter and Wilbur^{8b} again called attention to these same symptoms—anxiety and depression coupled with insomnia and nervousness. These authors stated the belief that the psychic manifestations are somehow directly related to the underlying disease process, and they have called attention to similar manifestations which occur in patients with hyperinsulinism due to adenoma of the islands. We have not paid especial attention to this problem, such manifestations have not been apparent in our patients. However, a disease process notorious for its repeated diagnostic frustrations lends itself well to a variety of symptoms in the neurotic sphere. As often as not the physician brands the patient with such a condition as neurotic and leaves him to his own resources. Anxiety and depression may naturally follow. Regardless of the mechanism, if such neurotic symptoms do continuously prove to be related to pancreatic malignancy they should be respected and should be entertained in the differential diagnosis of vague complaints referred to the upper part of the abdomen. In the presence of significant loss of weight, which is the rule in pancreatic malignancy, one should hesitate to ascribe too much neurotic significance to such symptoms, if they are present. Usually neurotic persons with conversion gastric symptoms maintain or even increase their weight, when loss in weight does occur it is small, except in cases of anorexia nervosa.

Venous Thrombosis—A clinical manifestation which merits emphasis is venous thrombosis. Thoenes¹³ called attention to this as an early manifestation of pancreatic malignancy in 3 cases which he reported. The thrombosis of the veins of the arm occurred before any other clinical evidence of the disease. Umlauf¹⁴ noted thrombosis of the veins of the thigh in 2 of 26 cases of pancreatic cancer and stated that it was allied with the cachectic state. Decreased coagulation time was noted in another case and thrombopenia in 2 others. Venous thrombosis occurred in 8 of our patients, in 6 it was directly related to pressure of the tumor, in 2 it occurred in the lower extremities probably secondary to pressure on the inferior vena cava and to venous stasis.

Roentgenologic Observations—Up to quite recently roentgen studies have been of limited value. In malignant diseases involving the head of the pancreas there is widening of the C angle of the duodenal curve.¹⁵ When there has been duodenal invasion, there may be duodenal obstruction. Dickson¹⁶ described loss of the valvulae conniventes when a tumor of the body of the pancreas implicated the transverse duodenum. Rigler¹⁷ found that a tumor of the body and tail tended to displace the stomach upward and forward and the transverse colon downward. When the mass of a pancreatic tumor is large it may exert pressure against the adjacent portion of the stomach, producing a filling defect and simulating the appearance of gastric malignancy. Hershenson¹⁸ recently developed a technic to demonstrate pancreatic tumors more clearly by an indirect method. The patient is placed on a tilted table, the abdomen resting against the table. The table is first placed in a vertical position and then is gradually lowered. No filling defect produced on the body of the stomach by a normal retrogastric structure is noted until the table is tilted nearly to its horizontal position, then a localized impression is produced on the midportion of the stomach. When a retrogastric tumor is present, such as a carcinoma of the body of the pancreas, the filling defect becomes noticeable at a point closer to the vertical plane.

13 Thoenes, E. Multiple Venethrombosen, ein bisher unbekanntes Frühsymptom bei Pankreaskarzinom, München med Wchnschr **79** 1677, 1932.

14 Umlauf, W. Thrombosen und Pankreaskarzinom, München med Wchnschr **80** 607, 1933.

15 Carty, J. R. Adenocarcinoma of the Head of the Pancreas, J. A. M. A. **96** 549 (Feb. 14) 1931.

16 Dickson, W. H. Diagnosis of Obscure Abdominal Lesions by the Roentgen Gastro-Intestinal Examination, Am J Roentgenol **10** 540, 1923.

17 Rigler, L. G. Diagnosis of Extra-Gastrointestinal Masses, Radiology **21** 229, 1933.

18 Hershenson, M. A. Carcinoma of the Tail and Body of the Pancreas. A Roentgenologic Technique for Its Demonstration, Am J Digest Dis & Nutrition **3** 835, 1937.

Still another technic for the indirect demonstration of pancreatic tumors has recently been developed by Engel and Lysholm¹⁹. On an empty stomach, the patient is given an ordinary effervescent powder with a mouthful of Vichy water. The patient is placed in the prone position, and immediately both lateral and anteroposterior roentgenograms are taken. These must be taken quickly, before the carbon dioxide has escaped from the stomach. Engel and Lysholm found that in 23 of 29 control subjects the retrogastric shadow, representing the tissue structures between the stomach and spine, was about the size of the corresponding vertebral body. Enlargement of the pancreas as by tumor was seen as an increase in the size of this retrogastric shadow. In some cases they could demonstrate local depressions into the inflated stomach, indicating localized tumor formations of smaller size. In stout emphysematous subjects the retrogastric shadow was found to be normally larger, probably as a result of the higher placement of the stomach and of the increase in retroperitoneal fat. Scholz and Pfeiffer²⁰ describe carcinoma of the tail of the pancreas simulating on roentgenologic examination a malignant change in the greater curvature of the stomach.

Another roentgen sign of possible value is worthy of mention. In a patient in our series a barium sulfate enema revealed considerable spasticity of the cecum and ascending colon. The roentgenologist of the hospital Dr. Marcy Sussman had made this observation in a previous case of pancreatic malignancy, and suggested that it might have diagnostic weight. Stern²¹ reported 2 cases of pancreatic malignancy and noted that there was abnormal retention of the barium sulfate, with considerable delay in the hepatic flexure. This was so contrary to the usual finding that he considered it of sufficient value to warrant consideration whenever pancreatic malignancy was suspected. In our group, 2 patients when given a barium sulfate meal showed prepyloric distortion. In each the head of the pancreas was also involved. Faintness or failure of visualization of the gallbladder after the use of dye was seen in 2 patients.

Hematologic Findings—It is significant that in only 2 instances of neoplasm of the pancreas was there anemia (hemoglobin below 70 per cent)—even though secondary metastases had already occurred in many instances.

The usual absence of secondary anemia in malignancy of the body and tail of the pancreas contrasts sharply with the almost universal

19 Engel, A., and Lysholm, E. A New Roentgenological Method of Pancreas Examination and Its Practical Results, *Acta radiol* **15** 635, 1934.

20 Scholz, T., and Pfeiffer, F. Roentgenologic Diagnosis of Carcinoma of the Tail of the Pancreas, *J. A. M. A.* **81** 275 (July 28) 1923.

21 Stern, R. Ueber die Diagnose des primären Pankreaskrebses, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **45** 71, 1938.

presence of secondary anemia in gastric malignancy at the stage of significant loss of weight

Leukocytosis was present in approximately 50 per cent of the cases. The greatest leukocytosis was found in those instances in which the carcinoma had already metastasized widely, especially those in which hemorrhagic ascites had developed or broken-down intraperitoneal tissue was present.

We have not studied the erythrocyte sedimentation rate in this disease. The rapid rate which others have stressed as of diagnostic importance may be related to malignancy as such, and may thus be of little value in differential diagnosis.

Special Laboratory Data—Of the procedures which have been reported as diagnostic aids, reliable estimations of blood amylase are sometimes significant. Elevated values were encountered once in our series (case 11). When there is malignant degeneration of pancreatic cysts subnormal values are more likely to be found. Blood lipase values were not abnormal in the cases of carcinoma of the body of the pancreas as reported by Comfort and Osterberg.²²

The absence of duodenal ferments is a valuable diagnostic finding, but such absence rarely occurs unless the head of the pancreas is involved. Likewise, steatorrhea usually occurs under that condition.

ILLUSTRATIVE CASES

Our material has demonstrated that malignancy of the body and tail of the pancreas may manifest itself in various forms.²³ Unfortunately we cannot describe a typical form or clinical syndrome. We are presenting cases which will illustrate some of the forms in which the disease may manifest itself, as follows:

- 1 Silent form. Initial manifestations after metastases have occurred, simulating, for example, disease of the chest. Thoracic pain present as a result of pleural metastases (case 2).
- 2 Simulation of partial high gastrointestinal obstruction, with duodenal stasis (case 10).
- 3 Simulation of gastrointestinal disease—gastric carcinoma or peptic ulcer. Gastrointestinal bleeding present (case 15).
- 4 Malignant degeneration of pancreatic cyst (case 19).
- 5 Peripheral venous thrombosis (case 9).

²² Comfort, M. W., and Osterberg, A. E. Lipase and Esterase in the Blood Serum, *J. Lab. & Clin. Med.* **20**: 271, 1934.

²³ Ransom, H. K. Carcinoma of the Body and Tail of the Pancreas, *Arch. Surg.* **30**: 584 (April) 1935. Duff, G. L. The Clinical and Pathological Features of Carcinoma of the Body and Tail of the Pancreas, *Bull. Johns Hopkins Hosp.* **65**: 69, 1939.

- 6 Intra-abdominal suppuration (case 17)
- 7 Lumbodorsal pain simulating spondylitis (case 11)
- 8 Pancreaticorenal form (cf table 3)

FORM 1 (case 2) —*Silent form—initial manifestations after metastases have occurred, simulating, for example, disease of the chest, thoracic pain present as a result of pleural metastases*

A male process server, 47 years of age, noted, three years previous to his admission to Mount Sinai Hospital, edema of the legs and feet and some dyspnea (The details of a prior hospitalization are not known) His immediate history dated back five months, to a night when he was awakened from sleep by severe pain in the lower right side of the chest Since that time the pain had been continuous and had become progressively more intense In the course of two months he had lost 40 pounds (18 Kg), this he attributed to the anorexia accompanying the pain He appeared chronically ill

Physical examination disclosed that the lungs were clear Fluoroscopic examination revealed no parenchymal lesion but some restriction in the descent of the right leaf of the diaphragm The upper part of the abdomen was rigid, chiefly in the right upper quadrant, where tenderness was elicited The lower edge of the liver was felt 3 fingerbreadths below the costal margin Rectal examination disclosed nothing of importance The hemoglobin was 72 per cent The white blood cells numbered 24,000, of which polymorphonuclear cells formed 88 per cent The stool was negative to the guaiac test for occult blood The temperature ranged between 99 and 102 F

The local signs, together with the restricted movement of the right leaf of the diaphragm, the blood count and the pyrexia, pointed to hepatic or subphrenic abscess, possibly secondary to neoplasm and most likely perforated No pus was obtained when aspiration of the right subphrenic space was attempted The general debility of the patient contraindicated surgical intervention The abdomen became distended and rigid throughout, and the patient died two weeks after admission to the hospital

Postmortem examination revealed 20 cc of a hemorrhagic fluid in the peritoneal cavity The cul-de-sac, which contained most of the hemorrhagic fluid, contained many flat nodules, which were over the peritoneal surface of the rectum The peritoneal aspect of the diaphragm was covered with numerous flat grayish nodules with hemorrhagic peripheral zones, and the liver also showed many umbilicated grayish nodules The pleura covering the lower lobe of the right lung was infiltrated by several flat neoplastic nodules The spleen weighed 110 Gm The splenic vein was ensheathed in tumor masses The head and first portion of the body of the pancreas were normal The remaining portion of the body was transformed into a large tumor, the size of a fist and quite firm, which was firmly adherent to the posterior wall of the stomach, into the lumen of which it bulged On section it was homogeneous, grayish, with hemorrhagic areas The regional lymph nodes were infiltrated by the neoplastic tissue, and the left adrenal gland was surrounded by it

FORM 2 (case 10) —*Simulation of partial high gastrointestinal obstruction, with duodenal stasis*

A 59 year old woman was admitted to the hospital in 1930, complaining that for about four years she had suffered from progressively severe belching Three months before admission she began to have epigastric discomfort and a feeling of distention after meals She had lost 25 pounds (11 Kg) in weight Pain of a

peculiar sort, located on both sides of the abdomen and radiating in parallel fashion from the nipples to the corresponding iliac crests, was present. In addition, the abdomen became rigid. She suffered excruciating pain in the back and was relieved only by lying prone.

On admission she was cachectic and weighed 85 pounds (38.5 Kg). Because of the peculiar reflex rigidity of the abdomen, it was impossible to palpate any viscera. The liver was percussed a hand's breadth below the costal margin. The hemoglobin was 81 per cent, and the white blood cells numbered 10,400. The Wassermann reaction of the blood was negative. The blood urea nitrogen was 10 mg per hundred cubic centimeters. The blood sugar was 235 mg per hundred cubic centimeters, the dextrose tolerance test showed a markedly decreased tolerance (fasting blood sugar, 200 mg, three hours after administration of dextrose, blood sugar 360 mg and urine sugar 10 per cent). On routine examination, no sugar was found in the urine, but albumin (3 plus) was present. The icterus index was 25. The bromsulphalein retention was 50 per cent at the end of thirty minutes. The stools contained no occult blood, but frequently large amounts of fat were present.

A diagnosis of metastatic neoplasm of the liver was made. To determine the primary focus, a gastrointestinal series of roentgenograms was made. The stomach was normal, but the whole length of the duodenum was dilated and reverse peristalsis was evident. There was retention of barium sulfate in the stomach and duodenum beyond the six hour period. The incomplete obstruction at the duodenojejunal angle was probably the basis for the long-continued belching after meals.

A diagnosis of carcinoma of the body and tail of the pancreas was suggested because of (1) the presence of chronic duodenal stasis with incomplete obstruction at the duodenojejunal angle, (2) the excess of fat in the stools, (3) the decreased tolerance for sugar, (4) the character of the pain and the relief in the prone position.

Two weeks after admission icterus appeared and persisted up to the time of death, one month later. Necropsy revealed a large scirrhous carcinoma of the body and tail of the pancreas, which had invaded the duodenojejunal angle, causing a circular constriction. The splenic vein was occluded completely. The spleen was moderately enlarged and indurated. The porta hepatis was invaded by tumor tissue and the lymph nodes in this region were enlarged, this had caused compression of the common bile duct, near its origin, and of the portal vein. The liver contained numerous metastases. Infiltration of the wall of the left ureter by tumor tissue had, by narrowing the lumen, produced a typical hydronephrosis of moderate degree, with widening of the calices, the pelvis and the proximal 2 inches (5 cm) of the ureter. The right ureter was not similarly involved. There was no ascites.

FORM 3 (case 15) —*Simulation of gastrointestinal disease—gastric carcinoma or peptic ulcer, gastrointestinal bleeding present*

The patient, a man of 37, complained of periumbilical pain, present for five months before admission. The pain occurred usually a few minutes after meals, lasted three to four hours and was relieved by the application of a hot water bag or by the ingestion of milk. Postprandial nausea and eructations were also present. Transient icterus, with temporary enlargement of the liver, had been present nine months before admission.

On physical examination no icterus was noted. There was slight epigastric spasm, more marked on the right, and also tenderness in the right upper quadrant of the abdomen, more marked over a slightly tender mass which extended 2 finger-

breadths below the liver and moved with respiration. Bilateral costovertebral tenderness was elicited. The hemoglobin was 98 per cent, the white blood cells numbered 13,000, of which 79 per cent were polymorphonuclear cells. The icterus index was 8, and the van den Bergh reaction was negative. The Wassermann reaction of the blood was negative. The blood amylase was 18 units. Examination of urine gave negative results. Of 9 tests for occult blood in the stools, 5 were positive, at irregular intervals. The Rehfuess test meal showed a maximum free acidity of 40. Gastrointestinal roentgenograms taken after the ingestion of barium sulfate showed several filling defects in the proximal half of the descending portion of the duodenum. There was marked delay in gastric motility, at the end of six hours, there was 75 per cent gastric retention. The middle of the descending portion of the duodenum was drawn to the right and apparently fixed. Roentgenograms made after the ingestion of dye failed to visualize the gallbladder on two occasions. Exploratory operation revealed an inoperable carcinoma of the body and head of the pancreas. It had already invaded the posterior aspect of the duodenum and the wall of the gallbladder.

FORM 4 (case 19) —*Malignant degeneration of a pancreatic cyst*

A 50 year old housewife was first admitted to the hospital in 1933, complaining of cramplike epigastric pain. Before her first admission to the hospital a large mass with a sharp edge had been noted in the left upper quadrant of the abdomen, it extended 4 cm below the costal margin. On the following day the mass was smaller and its edge indistinct, and the next day it had disappeared. At the time of admission the abdomen was slightly distended. There was tenderness in the epigastrium and left upper quadrant of the abdomen. However, no masses were felt. The hemoglobin was 88 per cent, the red blood cells numbered 5,350,000, the white blood cells numbered 5,000, of which 56 per cent were polymorphonuclear and 11 per cent eosinophilic. The stool was negative for occult blood. The free acidity of the gastric contents after the administration of histamine was 16 degrees. The Wassermann reaction of the blood was negative. The blood sugar was 110 mg per hundred cubic centimeters. The blood amylase was 64 units. Roentgenograms taken after the ingestion of barium sulfate showed a prepyloric spasm but no evidence of an intrinsic lesion in any part of the gastrointestinal tract. The stomach, however, seemed to be displaced by an extrinsic mass. While the patient was in the hospital a mass again became palpable in the left upper quadrant of the abdomen, just below the costal margin.

During the two years after the patient's discharge, several blood counts revealed persistent eosinophilia, the percentage of eosinophils ranging between 5 and 10. The patient continued to vomit intermittently and complained of a vague but steady ache in the left upper quadrant of the abdomen. Loss of weight was progressive, and at the time of her second admission she weighed 50 pounds (22.5 Kg) less than on the first admission. In the four weeks preceding her second admission the patient had marked anorexia and fever, with no chills.

Examination on admission revealed a large liver which extended 3 fingerbreadths below the costal margin. In the left upper quadrant of the abdomen was a large mass which extended down to the level of the umbilicus with respiration. Its surface was smooth and its consistency hard. There was tenderness on pressure over this area. There was no evidence of ascites. The pelvic and rectal examinations showed no abnormality. The hemoglobin was now 75 per cent, the red blood cells numbered 4,560,000. The white cells numbered 15,100, of which 64 per cent were polymorphonuclear and 9 per cent eosinophilic. The blood amylase was less than 1 unit. The icterus index was 9. The skin test and complement fixation test for echinococcus were negative.

Roentgenographic examination of the abdomen showed a large mass in the left upper quadrant, the lower portion of which reached the crest of the ilium. Pneumoperitoneum showed the spleen to be of normal size.

Vomiting soon set in and the patient's general condition became too poor to permit surgical exploration. Terminally phlebitis developed in the left leg. Necropsy revealed a large pancreatic cystadenocarcinoma with extensive metastases to the regional lymph nodes and liver. Lipomatosis of the tail of the pancreas, with atrophy of the pancreatic tissue, was apparent. When the pancreatic duct was explored, the probe entered the cyst. This served to explain the intermittent presence of an abdominal mass, suggesting that the cystic mass emptied itself through the duct. Other findings were thrombosis of the left femoral vein, embolism of the right pulmonary artery and pulmonary edema. Bronchopneumonia was also present and was the immediate cause of death.

FORM 5 (case 9) — *Peripheral venous thrombosis*

A housewife aged 65 entered the hospital and died after three days. Her illness had begun only seven weeks before, when swelling of the entire left lower extremity developed. Aside from some weakness, anorexia and marked constipation, the patient had been fairly well until one week before admission, when mild but persistent cough set in. Dizziness and increasing drowsiness were apparent the day before admission. The presenting symptom, coma, was associated with signs of bilateral involvement of the pyramidal tracts, spasticity being present on the left side and flaccidity on the right. Over the base of the right lung there was a sharply outlined area of dulness with diminished breath sounds. A large irregular liver was readily palpable. There was no icterus. The cerebrospinal fluid was under no increased pressure. It contained 13 white cells per cubic millimeter. Culture of the cerebrospinal fluid showed no bacteria, and the colloidal gold curves were normal. The blood urea nitrogen was 22 mg per hundred cubic centimeters, sugar, 145 mg, cholesterol, 280 mg. The urine was normal. The temperature ranged from 100 to 101 F.

Necropsy disclosed a scirrhous adenocarcinoma of the tail of the pancreas with metastases to the liver, lungs and pleura. There was a noncarcinomatous thrombosis of the left common iliac vein and almost all its branches. All the veins about the rectum and uterus were thrombosed. A well formed thrombus was seen projecting into the lumen of the inferior vena cava. The spleen was enlarged because of infarction and occlusion of the splenic vein by the encroaching tumor mass. This mass had also invaded the left adrenal and the left ureter, producing hydronephrosis on the left side. Infarcts of the lungs and kidneys and bronchopneumonia were also present. The brain disclosed no metastases or gross vascular lesions. Microscopically there were extensive areas of cortical softening.

FORM 6 (case 17) — *Intra-abdominal suppuration*

A 50 year old waiter was admitted to the hospital in 1933. For many years he had had recurrent attacks of diarrhea, with as many as ten bowel movements daily. The stool contained mucus but no blood or pus. A history of long-standing unproductive cough was elicited. About three weeks before admission he began to be troubled with pain in the right lumbar region, which became progressively more severe and which occasionally radiated down the right thigh to the knee. No urinary symptoms were associated with the pain. One week before admission there was soreness just below the ribs, and at this time the pain began to radiate upward into the chest on the right side and was aggravated by respiration and cough. There were progressive anorexia and a low grade fever. The patient lost 20 pounds (9 Kg) in weight. Six days before admission he had a severe

attack of pain in the right side of the abdomen, radiating to the spine and across to the left side of the abdomen. On admission the temperature was 106 F. There was mild generalized abdominal distention. The liver was palpable 4 fingerbreadths below the costal margin. The hemoglobin was 78 per cent, the white blood cells numbered 28,800, of which 88 per cent were polymorphonuclear forms. The blood urea nitrogen was 28 mg per hundred cubic centimeters, the blood cholesterol 180 mg and the cholesterol esters 37 mg. The icterus index was 12, the van den Bergh direct reaction was negative, and the indirect reaction was 1 500,000, with 0.2 mg of bilirubin. The Wassermann reaction of the blood was negative. The urine revealed no tyrosine. Roentgenograms showed the left kidney to be normal, there was marked ptosis of the right kidney, the lower pole being well below the iliac crest. There was marked enlargement of the spleen.

During the patient's stay in the hospital there was intermittent fever, the temperature varying between 100 and 103 F, with occasional rises to 104 or 105 F. Abdominal distention was persistent. There were occasional pain in the right upper quadrant of the abdomen and some tenderness over the enlarged liver. There were periods during which the patient's general condition greatly improved. Shortly afterward, however, the temperature would rise, the abdomen would again become more distended, and the appetite would diminish. Edema of the sacrum and extremities, which was only moderately relieved by mercurial diuretics, persisted in varying degrees until death. Cultures of blood taken just before chills were experienced were reported negative.

The patient died two months after admission. Necropsy disclosed an adenocarcinoma of the body of the pancreas with metastases to the adjacent lymph nodes and liver, a localized purulent peritonitis with peripancreatic abscess perforating into the stomach, hepatic abscess with perforation into the peritoneal cavity, and a loculated right subdiaphragmatic abscess. Bronchostenosis was present in the lobes of the left lung, but it was not due to carcinomatous metastases.

FORM 7 (case 11)—*Lumbodorsal pain simulating spondylitis*

A 52 year old counterman had a history of long-standing heartburn, constipation and flatulence. He entered the hospital in 1933 after six weeks of severe sharp constant pain in the region of the thoracic spine, which had soon encircled the left flank and hypochondrium, reaching the xiphoid cartilage. The pain also extended up into the left axilla. There had been anorexia and a loss of 15 pounds (7 Kg) in weight.

Physical examination revealed a well developed man, somewhat plethoric. The blood pressure was 210 systolic and 122 diastolic. The hemoglobin was 82 per cent, the white blood cells numbered 6,200, of which the polymorphonuclear forms numbered 76 per cent. The cinchophen oxidation test showed evidence of marked disturbance in the function of the liver. The Rehfuess test meal showed a total acidity of 42 and a free acidity of 22. The Wassermann reaction of the blood was negative. Roentgen examination of the spine showed moderate arthritic changes consistent with the patient's age. Roentgenograms at first failed to show the gallbladder, and subsequent visualization of this organ was faint, the gastrointestinal tract appeared to be normal, the chest showed no parenchymal lesion.

The blood amylase level was 175 units. The Janney dextrose tolerance test showed diminished tolerance for sugar on two occasions, on one of these the fasting level was 85 mg per hundred cubic centimeters, at the end of one and a half hours it was 235 mg, at the end of three hours it was 300 mg, and at the end of five hours it was 280 mg. On two occasions examination of the duodenal

contents obtained by drainage showed no trypsin. The blood cholesterol was 340 mg, and the cholesterol esters, 170 mg. Because of the amylase level and the dextrose tolerance curve the patient was thought to be suffering from low grade pancreatitis, and cholecystectomy was advised, thus the patient refused.

He was readmitted to the hospital two months later with a recurrence of his original pain. An exploratory operation was done, and the pancreas was found to be the seat of a hard tumor, evidently a carcinoma. The liver was normal in consistency but shrunken. The gallbladder was moderately enlarged and contained 3 ounces (88.5 cc) of thick, concentrated bile. The bile ducts appeared dilated. Cholecystogastrostomy was done. The patient left the hospital, and follow-up records indicated that he died a month after discharge.

SUMMARY

Nineteen cases of primary carcinoma of the body and tail of the pancreas, in which the diagnosis was confirmed by laparotomy or by necropsy, have been observed during a period of ten years.

The symptom complexes that have been encountered are presented. They are explained on the basis of actual neoplastic invasion, local and distant metastases or mechanical pressure.

As a result of our analysis the following clinical signs and symptoms assume diagnostic significance:

1. Rapid loss of weight unaccounted for by diabetes, hyperthyroidism, tuberculosis, anorexia nervosa, spure or demonstrable malignant tumor.

2. Anorexia.

3. Noncolicky pain in the abdomen—either diffuse or in the upper portion—radiating to the lumbar region, unrelated to the digestive cycle, unrelieved by food, often nocturnal and relieved by change in posture.

4. Absence of anemia.

5. Absence of occult blood in the stool (unless the tumor has invaded the duodenum or stomach).

6. Disturbed carbohydrate tolerance manifested by glycosuria, hyperglycemia or a dextrose tolerance curve of the diabetic type.

7. Atypical roentgen findings in the duodenum or stomach.

8. Elevation of the blood amylase.

9. Hemorrhagic ascites.

10. Peripheral venous thrombosis.

The absence of secondary anemia and of occult blood in the stool and the presence of significant loss of weight sharply differentiate malignant growth of the body and tail of the pancreas from gastric carcinoma, in which significant loss of weight is invariably coupled with secondary anemia and occult blood in the stool.

UREA REABSORPTION AND RELATION BETWEEN CREATININE AND UREA CLEARANCE IN RENAL DISEASE

AARON ARKIN, M D, P H D

Associate Professor of Medicine, Rush Medical College, University of
Chicago, and Chairman of the Department of Medicine,
Cook County Graduate School of Medicine

AND

HANS POPPER, M D *

CHICAGO

Richards¹ has proved by examinations of the glomerular urine of the frog that urea is filtered through the glomerular loops

The reabsorption of urea in the tubules was demonstrated by investigations based on the theory of Cushny and of Rehberg² Such substances as creatinine are filtered through the glomeruli but are not secreted or reabsorbed in the tubules With this in mind, one is able to observe the pathway of other substances in the kidney

The exogenous creatinine clearance method used by Rehberg for the determination of the filtration rate gives reliable results in the dog but not in man (Smith,³ Shannon⁴) In human subjects administration of creatinine causes an increase in the clearance as a result of secretion Therefore, the inulin clearance method was employed in the calculation of the filtration rate (Shannon and Smith,⁵ Richards and his associates⁶) The endogenous creatinine clearance test probably does not involve this error and gives a more reliable measure of glomerular filtration (Popper and Mandel,⁷ Miller and Winkler⁸), as the values are

* Research Fellow, Cook County Graduate School of Medicine

From the Cook County Graduate School of Medicine and the Cook County Hospital, Medical Service of Dr Aaron Arkin

1 Richards, A N Proc Roy Soc, London, s B **126** 398, 1938

2 Rehberg, P B Biochem J **20** 447, 1926

3 Smith, H W The Physiology of the Kidney, New York, Oxford University Press, 1937

4 Shannon, J A J Clin Investigation **14** 403, 1935

5 Shannon, J A, and Smith, H W J Clin Investigation **14** 393, 1935

6 Richards, A N, Westfall, B B, and Pott, P A Proc Soc Exper Biol & Med **32** 73, 1934

7 Popper, H, and Mandel, E Ergebn d inn Med u Kinderh **53**:685, 1937

8 Miller, B F, and Winkler, A W J Clin Investigation **17** 31, 1938

in close accord with those for the inulin clearance (Steinitz and Turkand⁹)

From the theoretic viewpoint for measurement of the filtration rate the inulin clearance test is superior to the endogenous creatinine clearance test. However, the inulin clearance test involves considerable technical difficulty and is not as readily adaptable to the study of a large amount of clinical material as is the test for creatinine clearance, which can be used for routine work¹⁰

A comparison of the urine-plasma ratio of urea with that of creatinine or inulin has been made by many authors. Some¹¹ compared the clearance of exogenous creatinine with that of urea in man, others made similar studies in dogs,¹² rabbits,¹³ sheep¹⁴ and chickens¹⁵ Winkler and Parra¹⁶ and Chasis and Smith¹⁷ used the inulin clearance for comparison, and Ferro-Luzzi¹⁸ published data concerning the endogenous creatinine clearance.

All these examinations showed the urea clearance to be somewhat lower than the creatinine clearance or the glomerular filtration rate, usually 30 to 70 per cent of the latter. This ratio may vary considerably and may rise to 100 per cent, even in normal persons or animals, especially when there is marked diuresis. The maximal urea clearance test of Van Slyke, with a flow of urine of over 2 cc per minute, demon-

9 Steinitz, K., and Turkand, H. *Tib fak mec*, Istanbul Univ **2** 1005, 1939

10 Popper, H. *Klin Wchnschr* **16** 1454, 1937

11 (a) Covian, C. G., and Rehberg, P. B. *Skandinav Arch f Physiol* **75** 21, 1936 (b) Keith, N. M., Power, M. H., and Petersen, R. D. *Am J Physiol* **108** 221, 1934 (c) Bings, J., and Bjering, T. *Acta med Skandinav* **93** 318, 1937 (d) Hayman, J. M., Jr., Halsted, J. A., and Seyler, L. E. *J Clin Investigation* **12** 861, 1933 (e) Cope, C. L. *Quart J Med* **24** 567, 1931 (f) Ellis, L. B., and Weiss, S. *Am J M Sc* **186** 242, 1933, Renal Function in Arterial Hypertension, *J A M A* **100** 875 (March 25) 1933 (g) White, H. L., and Heinbecker, P. *Am J Physiol* **123** 566, 1938 (h) McCance, R. A., and Widdowson, E. M. *J Physiol* **91** 222, 1937 (i) Rehberg² (j) Popper and Mandel⁷

12 (a) Jolliffe, N., and Smith, H. W. *Am J Physiol* **99** 101, 1931 (b) Shannon, J. A. *ibid* **117** 206, 1936, **123** 182, 1938 (c) Kay, W. W., and Sheehan, H. L. *J Physiol* **79** 359, 1933 (d) Van Slyke, D. D., Hiller, A., and Miller, B. F. *Am J Physiol* **113** 611, 1935 (e) Hayman, J. M., Jr., Shumway, N. P., Dumke, P., and Miller, M. *J Clin Investigation* **18** 195, 1939 (f) Alving, A. S., and Gordon, W. *J Biol Chem* **120** 103, 1937

13 Kaplan, B. I., and Smith, H. W. *Am J Physiol* **113** 354, 1935

14 Shannon, J. A. *Proc Soc Exper Biol & Med* **37** 379, 1937

15 Pitts, R. F., and Korr, J. M. *J Cell & Comp Physiol* **11** 117, 1938 Shannon, J. A. *ibid* **11** 123, 1938

16 Winkler, A. W., and Parra, J. P. *J Clin Investigation* **16** 869, 1937

17 Chasis, H., and Smith, H. W. *J Clin Investigation* **17** 347, 1938

18 Ferro-Luzzi, G. *Ztschr f d ges exper Med* **94** 708, 1934

strates the same fact, as then the urea clearance is independent of the flow of urine and corresponds roughly with the filtration rate

According to Rehberg, the variations in reabsorption of urea depend on physical forces within the tubular system. It was previously assumed⁷ that the tubular epithelium forms a barrier which regulates the composition of the reabsorbed fluid streaming to the reabsorbing capillaries. The selective permeability of the tubular epithelium undergoes constant changes according to the general needs of the organism. It prevents the back flow of part of the filtered urea, thus concentrating it in the urine. Damage of the tubular cells may impair the function of the barrier and increase the back flow, causing reabsorption uremia (Ferro-Luzzi¹⁸). These findings correspond with the results of animal experiments performed by Yamaguchi,¹⁹ which revealed the pathologic reabsorption of congo red, creatinine and albumin by damaged tubules. This conception being correct, the reabsorption of urea should increase in the damaged kidney. In contrast, it was assumed²⁰ that decreased filtration is compensated for by decreased reabsorption of urea in order to increase the urinary output and to prevent retention. This assumption is in accordance with the results of Smith and Shannon.

In order to estimate the amount of reabsorption of urea in a damaged kidney we compared the clearance of urea and that of creatinine in normal and in pathologic conditions. As the method of Popper, Mandel and Mayer²¹ permits an exact determination of creatinine at normal blood levels, oral administration could be omitted.

METHOD

Fasting patients were catheterized, and the urine was discarded. They remained in bed, and two to three hours later the bladder was catheterized again and the sample of urine examined. In men a permanent catheter was usually inserted, and in a few cases voluntary emptying of the bladder was permitted. Blood was drawn into a tube containing oxalate. Sometimes two test periods were combined in one day. When creatinine is not administered the amount in the blood does not change, and one determination is sufficient.

The creatinine content of urine and of blood plasma was determined by the absolute colorimetric method,²¹ and the urea content, with urease and micro-distillation according to the method of Rappaport and Gutmann.²² The normal creatinine content of the blood varies between 0.6 and 1 mg per hundred cubic centimeters. Even a slight increase over 1 mg indicates glomerular insufficiency.²³

19 Yamaguchi, T. *Tohoku J. Exper. Med.* **18** 392, 1931. Shoji, T., and Takeda, K. *ibid.* **26** 592, 1935.

20 Popper, H., and Brod, J. *Ztschr. f. klin. Med.* **134** 196, 1938.

21 Popper, H., Mandel, E., and Mayer, H. *Biochem. Ztschr.* **291** 354, 1937.

22 Rappaport, F., and Gutmann, M. *Klin. Wchnschr.* **14** 1325, 1935.

23 Popper, H., Mandel, E., and Mayer, H. *Ztschr. f. klin. Med.* **133** 56, 1937.

Glomerular filtrate and resorbate were calculated according to the formula of Rehberg.² The concentration index (a measure of the concentration of the urine) equals the urine-plasma ratio of creatinine. Excretion of urea was indicated as the excretion percentage, the amount of urea appearing in the urine in per cent proportion to the urea filtered in the glomeruli. It corresponds with the urea-creatinine clearance ratio

$$E_u = \frac{\frac{\text{urine urea}}{\text{plasma urea}}}{\frac{\text{urine creatinine}}{\text{plasma creatinine}}} \times 100$$

RESULTS

The material includes 191 determinations in 92 cases. Many patients were examined several times on different days in the course of the disease. Table 1 shows the types of cases used. Convalescent patients or those without any pathologic conditions of the kidneys were used as controls. Listed as cases of extrarenal glomerular insufficiency are those in which there was an increase in the creatinine level due to changes in the general circulation without any specific pathologic conditions of the kidneys, such as are found in heart failure, infections and hypochloremia. In the group of cases of hypertension the different types of vascular disease of the kidneys are combined: essential hypertension and benign and malignant nephrosclerosis. In the group of cases of acute nephritis an instance of extraglomerular nephritis is included in which the course was progressive and death resulted from

TABLE 1—*Excretion Percentage of Urea in Diseases of the Kidneys*

Condition	Number of Cases	Number of Examinations	Excretion Percentage of Urea		
			Maximum	Minimum	Average
Normal	42	76	69.2	6.8	26.4
Acute nephritis	7	12	14.8	3.4	4.6
Chronic nephritis	8	17	92.5	15.8	49.1
Hypertension	15	39	101	3.0	35.5
Nephrosis	4	13	54.7	24.8	35.1
Pyelonephritis	6	26	176	34.8	67.3
Extrarenal insufficiency	6	8	90	13.7	41.2

uremia within a few days. Under chronic nephritis the severe and the mild forms are combined. The group of cases of pyelonephritis comprises those of contracted kidney due to chronic pyelonephritis, in which the condition is often difficult to differentiate from chronic nephritis. In the cases of a more severe form the diagnosis was often confirmed by autopsy.

Table 1 shows that the excretion percentage of urea in normal persons varies between 6.8 and 69.2, with an average of 26.4 for 76 examinations in 42 cases. In all cases in which there were pathologic conditions the average was higher. In nephrosis the increase is not significant, it is higher in hypertension and in acute nephritis. The difference is marked in the diseases with contraction of the kidney,

such as chronic nephritis or pyelonephritic contracted kidney. The extra-renal glomerular insufficiency shows a slight increase as compared with the normal.

As important as the average increase is the elevation of the excretion percentage over 100 in some conditions. This indicates that the urea clearance is higher than the creatinine clearance. This elevation is far in excess of any error of the method. Repetition of the E_U on the same day shows it to be constant. In examinations with intervals of several days a definite variation occurs (table 2).

TABLE 2—*Variations in Excretion Percentage of Urea on Different Days*

Patient	Date	Urinary Output, Cc per Min	Urine Creatinine, Mg per 100 Cc	Plasma Creatinine, Mg per 100 Cc	Concentration Index	Creatinine Clearance, Cc per Min	Urea Nitrogen in Urine, Mg per 100 Cc	Urea Nitrogen in Plasma, Mg per 100 Cc	Excretion Percentage of Urea
J	12/16	0.38	308	3.36	91.6	34.5	1,537	18.6	90
	12/18	0.57	190	1.68	113	64.4	1,212	34.1	31.3
		0.56	200	1.68	119	67.1	1,258	34.1	30.8
	12/20	0.70	144	0.97	148.6	118	1,351	32.8	27.8
	12/23	0.38	228	2.16	105.3	40.6	699	25.1	27.5
	1/4	1.14	83	1.06	78.3	89.4	513	13.9	47
	1/8	0.61	186	0.93	200	121.6	851	12.7	33.6
H	12/9	0.83	93	2.40	38.7	32.02	373	32.6	29.5
	12/10	0.77	83	2.29	36.2	27.98	453	27.3	45.9
	12/14	0.58	133	2.59	45.01	26.5	536	28.0	42.5
	12/23	0.77	164	5.72	28.3	21.8	792	72.7	38.6
	1/3	1.25	59.1	4.04	14.4	18.03	330	30.3	87
	1/5	0.39	162	4.44	36.6	14.03	559	41.9	36.4
	1/8	0.66	117	3.96	29.6	19.7	331	48.9	23
		0.66	115	3.96	29.1	19.3	331	48.9	23.2
	1/13	3	68	3.36	22.9	59.8	234	25.6	45.8
		0.91	78	3.36	22.9	21.0	279	25.6	47.5

A plot of the E_U and the urinary output shows a slight parallelism between increase of urine flow and E_U . However, only in persons with normal kidneys is a low urinary output combined with a low E_U , whereas in persons with pathologic conditions it may correspond with a high E_U .

Closer uniformity in the plot is obtained by comparing the E_U with the concentration index, as already done by Shannon^{12b} and Chasis and Smith¹⁷. Figure 1 shows a high concentration index typically combined with a low E_U . An index of over 250 never corresponds with an E_U over 25, while with an index below 60 the E_U is never below 20 and may go as high as 100 or more. The characteristic line of Shannon and Smith, with an angle around the index of 20, is to be seen despite the extensive scattering due to the variety of pathologic conditions. Extra-renal glomerular insufficiency, nephrosis, acute nephritis and benign nephrosclerosis reveal rather normal conditions, in contrast to those in cases of severe renal damage, such as chronic nephritis, pyelonephritic contracted kidney, malignant nephrosclerosis and acute extraglomerular nephritis (1 case).

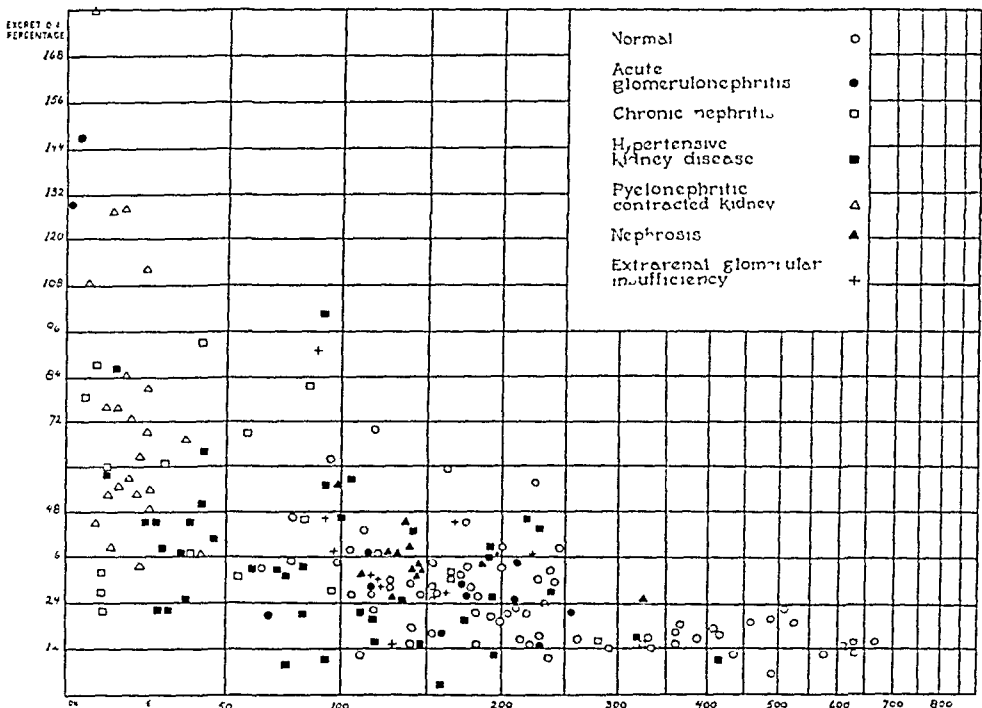


Fig 1—Logarithmic plot of excretion percentage of urea and concentration index in various diseases of the kidney

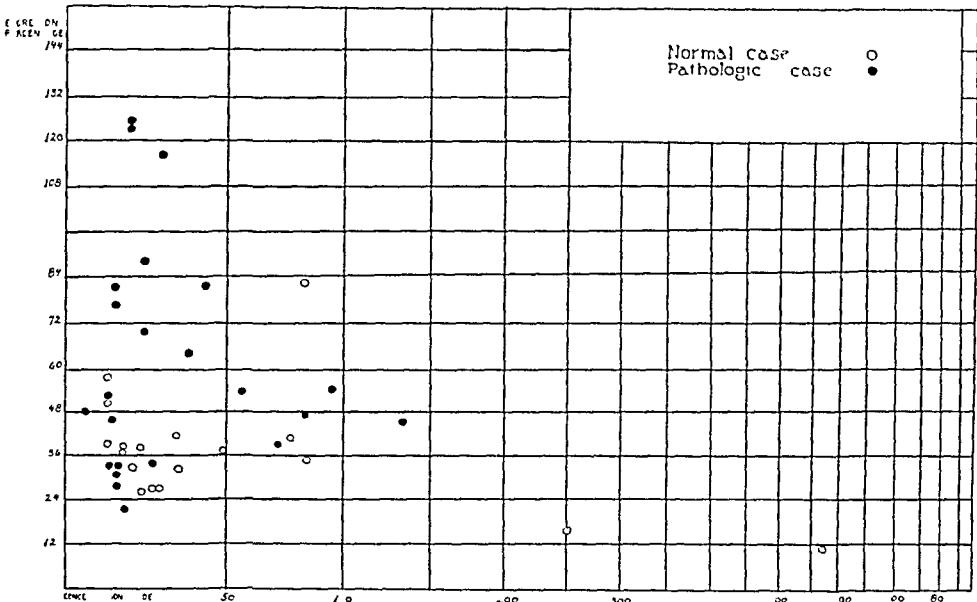


Fig 2—Logarithmic plot of excretion percentage of urea and concentration index in 7 patients with normal or slightly damaged kidneys. Each person received 1,500 cc of fluid and excreted most of this amount within four hours

Figure 1 confirms Smith and Shannon's finding that there is a direct connection between diminution of the concentration of the urine and increase of the E_u . We obtained a lower index in normal persons by forcing diuresis by the administration of 1,500 cc of fluid, the same was done in some cases of slight renal involvement. Figure 2 reveals the results of 8 examinations in 7 cases.

In accordance with Smith and Shannon, a falling index leads to an increase of the E_t and thus to an approximation of the urea and the creatinine clearance. However, the decrease in the concentration of the urine may not be the only decisive factor for a low E_u , since in patients with pathologic conditions the E_u is much higher with the same index than in normal persons, as seen by a comparison of figures 1 and 2. This suggests a second factor independent of the low concentration, the presence of a disease of the kidneys.

The plasma creatinine is a measure of renal function, as its increase indicates the degree of impairment in glomerular circulation and filtration. Figure 3 shows a definite connection between the E_u and the creatinine level. With normal or slightly damaged renal function the E_u is low in fasting patients. With the creatinine content below 1 mg per hundred cubic centimeters the E_u never exceeds 62. With slightly increased creatinine, up to 2 mg, the E_u shows a slight tendency to rise. However, in patients with acute nephritis, nephrosis and extrarenal glomerular insufficiency and in some of the hypertensive patients the values are within normal range. With further increase in creatinine the tendency for the E_u to rise is more definite but not uniform. Next to the highest E_t , together with the highest creatinine level, was found in the patient with extraglomerular acute nephritis who was twice examined. The rise does not take place in all cases in which there is a high creatinine content, however, we never observed an E_u below 20 if the creatinine level was over 2 mg.

As the glomerular filtration rate is related to the plasma creatinine level, there is an increase in the E_u with a decrease in creatinine clearance. In nephrosis the E_u is normal despite the decreased filtration rate.

As decreased reabsorption in fasting persons is a sign of severe disease of the kidneys, it is usually combined with an increasing E_u . Among the patients with diminished reabsorption during fasting those with pyelonephritis show the highest E_u . Thus there is a tendency for the E_u to be low when the filtration and reabsorption rates are reduced.

COMMENT

The examinations show, in accordance with the reports in the literature, the variations in the excreted urea as compared with the filtered urea, and thus the variations in reabsorption of urea. Two factors may influence the reabsorption of urea. The first factor is the amount of diuresis, which is in relation to the degree of concentration of the urine. According to Smith and Shannon, this is explained by physical forces, such as speed of the flow of urine in the tubules. The second factor

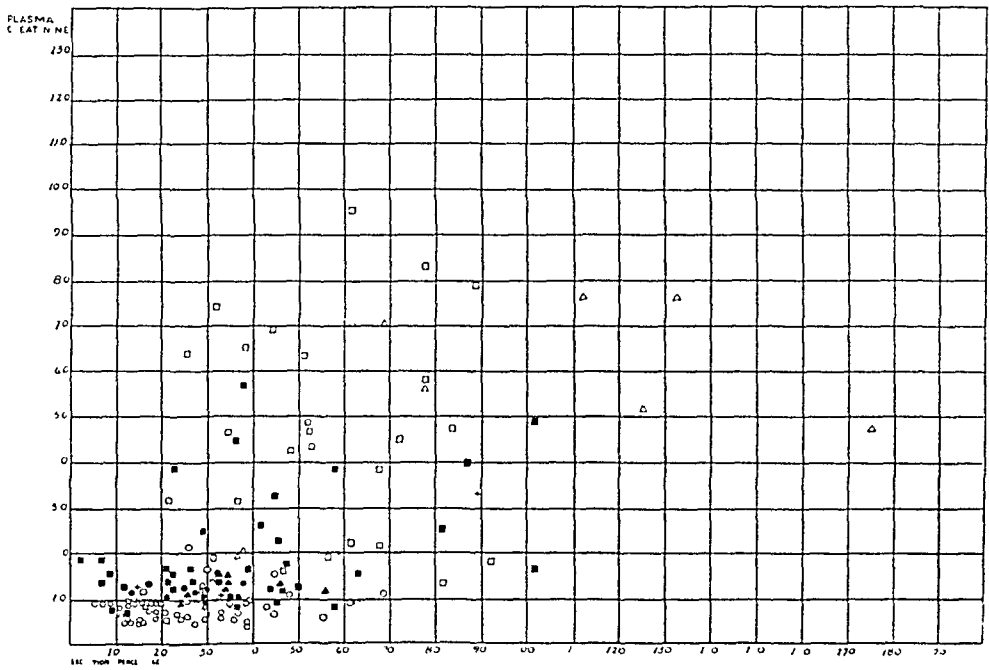


Fig 3—Plot of the excretion percentage of urea against the plasma creatinine (milligram per thousand cubic centimeters) in normal persons and in those with pathologic conditions

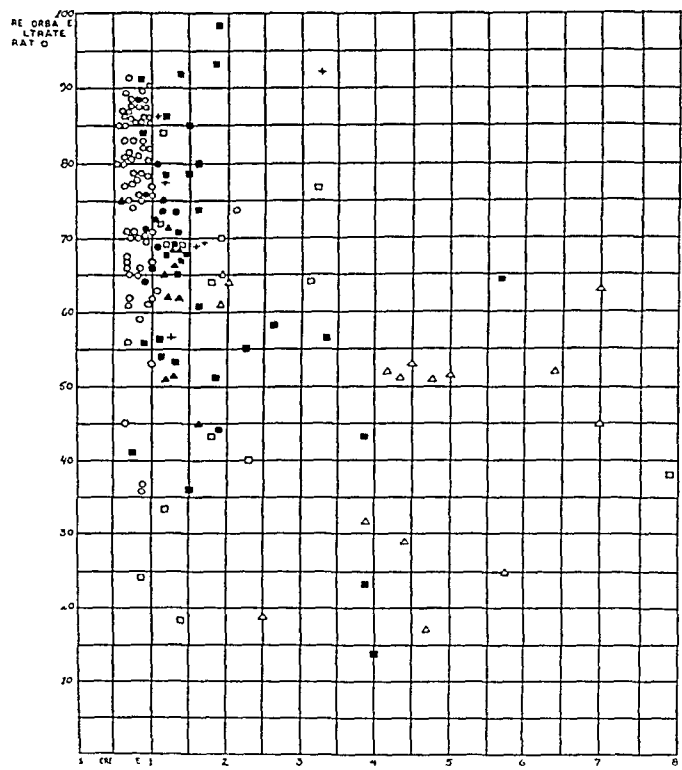


Fig 4—Plot of the resorbate-filtrate ratio of urea against the plasma creatinine in normal persons and in those with pathologic conditions

is the presence of severe damage to the kidney. Patients with glomerular damage of slighter degree and moderately increased plasma creatinine show nearly normal urea reabsorption, as in extrarenal glomerular insufficiency, benign nephrosclerosis, acute nephritis or nephrosis, which now is considered to be a primary glomerular condition.²⁵ In the uremic kidney diseases, with decreased flow of blood and fluid through the organ (dehydration of the kidney tissue), the urea reabsorption is much diminished, as in chronic nephritis, malignant hypertension, acute extraglomerular nephritis and pyelonephritic contracted kidney. The simplest explanation for the decreased urea reabsorption in these cases is the decreased reabsorption of water.

In a prior study one of us tried to calculate the content of urea in the reabsorbate. The calculation is not logical, since it is now believed that the reabsorbed fluid does not have a uniform urea content. Urea and water are not reabsorbed equally in the same place (Keller,²⁶ Smith and Shannon). However, in order to answer the question whether the decrease in urea reabsorption depends only on the decreased back flow of water, the comparison of the urea content of a hypothetical uniform reabsorbate with that of the filtrate or plasma is significant. The calculation is made according to the following formulas,² which point out the reabsorbate-filtrate ratio.

$$\text{Reabsorbate urea} = 100 \frac{(\text{plasma urea} \times \text{filtration rate}) - (\text{urine urea} \times \text{urinary output})}{\text{reabsorption rate}}$$

$$\text{Reabsorbate-filtrate ratio } (U_R) = \frac{\text{reabsorbate urea}}{\text{plasma urea}} \times 100$$

U_R is a measure of the antiosmotic force effective in the tubules, which force is stronger when the ratio is lower. A plot of the U_R against the plasma creatinine as a measure of the involvement of the kidney reveals a definite decrease in the U_R in cases of pathologic kidneys. In normal persons the average is about 72. A decrease corresponds with the degree of kidney disease and is moderate with slightly impaired glomerular function.

The relatively low urea content of the hypothetical reabsorbate as compared with that of the filtrate in kidney disease indicates strong antiosmotic forces effective at the epithelial barrier against the attempted backward diffusion of urea. Thus, the low urea reabsorption is explained not only by a decreased back flow of fluid but by an actual counteraction. Increased reabsorption can therefore be excluded, and we join Smith in not recognizing the association of reabsorption uremia with diseases of the kidneys.

25 Randerath, E. *Ergebn d allg Path u path Anat* **32** 91, 1937. Bell, E. T. *Am J Path* **14** 691, 1938.

26 Keller, R. *Der elektrische Faktor der Nierenarbeit*, Mährisch-Ostrau, Verlag Julius Kittls Nachfolger, 1933.

Important are the few examples in which the E_u is over 100. If more urea is excreted than filtered, secretion of urea may be assumed. It could be argued that in the damaged kidney a reabsorption of creatinine exceeding that of urea takes place, which would explain the relatively low creatinine clearance. This is not probable from a physical point of view, as the diffusion gradient of urea is higher than that of creatinine.²⁷ Recent studies of McCance and Widdowson²⁸ have shown a pathologic back flow of creatinine in cases of diabetic coma. This is not likely in diseases of the kidney. An approximation of urea clearance to creatinine clearance, or even an excess of urea clearance, is found in several cases of severe kidney damage recorded in the tables of Hayman, Halsted and Seyler^{11d} and also in those of Ellis and Weiss.^{11f} Both groups of investigators administered creatinine, thus raising the creatinine clearance above the filtration rate, and recorded the standard urea clearance, which was lower than the original urea clearance. Despite that, the urine plasma ratio of urea was in some cases higher than that of creatinine. The possibility of urea secretion in man can therefore be assumed. This fact was also proved in amphibians by Marshall³⁰ and by Walker and Hudson.³¹ We have found that a rise of the urea clearance over the creatinine clearance occurs in rabbits after injection of urine or certain poisons up the ureter with high pressure. The same occurs after selective destruction of the renal pyramid by vinylamine poisoning.

What role may urea secretion play in diseases of the human kidney? With regard to urea reabsorption, we have considered that antiosmotic forces are stronger than normal in cases in which there is severe damage to the kidneys.

If in a pathologic condition a function is increased, a compensatory mechanism must be assumed. This assumption agrees with our previous view that the decreased reabsorption with impaired filtration is an attempt to reduce urea retention. Even in the presence of severe damage to the kidney the epithelium of the still functioning nephrons shows an increased function of the barrier. Disturbed power of concentration of the kidney may be due not to impaired tubular function.

27 Bunim, J. J., Smith, W. W., and Smith, H. W. *J. Biol. Chem.* **118** 667, 1937.

28 McCance, R. A., and Widdowson, E. M. *J. Physiol.* **95** 36, 1939.

29 Footnote deleted.

30 Marshall, E. K. *J. Cell & Comp. Physiol.* **2** 349, 1932.

31 Walker, A. M., and Hudson, C. L. *Am. J. Physiol.* **118** 153, 1937.

32 Footnote deleted.

but to the diminution in reabsorption of water, which is explained by the distribution of the reabsorbing medullary vessels³³ and the dehydration of the kidney tissue

SUMMARY

The clearance of urea and that of endogenous creatinine were compared in 87 cases of normal and of pathologic conditions in order to estimate the reabsorption of urea

Urea reabsorption is constant during the same day, but not on different days. It is slightly diminished during fasting in moderate glomerular disorders, such as acute glomerulonephritis, benign hypertension, nephrosis and extrarenal glomerular insufficiency. It is markedly diminished in many cases of severe damage to the kidneys, as in chronic nephritis, malignant hypertension, pyelonephritic contracted kidney and extraglomerular acute nephritis (1 case). The lowest rate of reabsorption was found in pyelonephritic contracted kidney.

The decrease in urea reabsorption, usually combined with disturbed filtration and reabsorption of water, may depend on two factors: the decrease in the urinary concentration and the presence of damage to the kidneys.

With severest damage to the kidneys the urea clearance may exceed the creatinine clearance. This may be interpreted as an indication of urea secretion.

Uremia due to reabsorption in renal disease does not exist. On the contrary, stronger antiosmotic forces are effective at the tubular barrier against the back flow of urea. This mechanism is probably compensatory in order to prevent urea retention with decreased filtration.

33 Fuchs, F., and Popper, H. *Ergebn d inn Med u Kinderh* **54** 1, 1938

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

WILLIAM S McCANN, M D

ROCHESTER, N Y

During the past year the major efforts of investigators in this field have been concentrated on the question of the renal factor in hypertension. The recent impetus to investigation has come from the work of Goldblatt, which has been discussed in previous reviews. As one might have supposed, search of the literature has brought to light prior discoveries of similar import which have been passed over and forgotten because their significance was not appreciated at the time they were made. Such discoveries in no way diminish the credit that is due Goldblatt, for, after all, they would have remained forgotten had it not been for the revival of interest aroused by his work.

In 1909 Theodore Janeway¹ published a brief note on the changes in blood pressure following the reduction of the renal arterial circulation. He observed the blood pressure of dogs before and after ligation of branches of the renal arteries by Alexis Carrel. Janeway used a modification of the Riva-Rocci sphygmomanometer. Rises in blood pressure were noted after the ligations. One of the 5 dogs which survived showed a rise of blood pressure from 110 to 150 mm of mercury systolic and from 80 to 110 diastolic. The urine of this dog was free from albumin. Another of these dogs was observed to show a much greater rise in pressure, but the urine of this dog contained albumin, casts and red corpuscles.

Another instance in which search of the literature has brought forgotten work to light is to be found in the report of Tigerstedt and Bergmann,² who in 1898 discovered the pressor substance in the kidney and named it "renin." This substance, as originally described by these

From the Department of Medicine of the University of Rochester School of Medicine and Dentistry and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals

1 Janeway, T. Note on Blood Pressure Changes Following Reduction of Renal Arterial Circulation, *Proc Soc Exper Biol & Med* 6 109, 1909

2 Tigerstedt, R., and Bergmann, P. G. Niere und Kreislauf, *Skandinav Arch f Physiol* 8 223, 1898

workers, appears to be identical with the pressor substance to which the hypertension of renal ischemia is now attributed

Still another instance concerns the production of nephritis by the use of heterologous nephrotoxic serums, as recently described by Masugi and by Smadel. In 1900, however, Lindemann³ produced a nephrotoxic serum from guinea pigs which had been given injections of emulsions of rabbit kidney. When injected into rabbits this serum produced profound disintegration of the renal tubules, no specific alteration of the glomeruli being observed. In this respect the experimental nephritis differed from that more recently described by Smadel, a condition which has proved to be true glomerular nephritis. Nevertheless, Lindemann deserves credit for the use of cytologic antisera for the production of an experimental disease.

RENIN

To return to the question of the renal pressor substance, a number of investigators have been engaged in devising methods for the extraction and purification of renin. Tigerstedt and Bergmann had used simple saline extracts. They believed the pressor substance to be a protein. Boylston, McEwen and Ivy⁴ were unable to obtain it by perfusion of ischemic kidneys with Locke's solution. However, Fasciolo, Houssay and Taquini⁵ were able to demonstrate its presence in the blood of the renal vein by testing for vasoconstrictor effects on the toad *Bufo arenarum* Hensel. Saline extracts of ischemic dog kidneys and of kidneys of human subjects with hypertension were found to yield greater pressor effects than similar extracts of normal kidneys by Prinzmetal, Friedman and Abramson⁶. The blood of patients with hypertension when transfused into those with normal pressures did not exhibit any pressor effects, according to the observations of Friedman and Prinzmetal⁷. When saline extracts were subjected to pie-

3 Lindemann, W. Sur le mode d'action de certains poisons rénaux, *Ann Inst Pasteur* **14** 49, 1900

4 Boylston, G. A., McEwen, E. G., and Ivy, A. C. A Pressor Substance Is Not Present in the Perfusate of Ischemic Kidneys, *Proc Soc Exper Biol & Med* **39** 559, 1938

5 Fasciolo, J. C., Houssay, B. A., and Taquini, A. C. The Blood Pressure Raising Secretion of the Ischemic Kidney, *J Physiol* **94**.281, 1938

6 Prinzmetal, M., Friedman, B., and Abramson, D. I. The Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, *Ann Int Med* **12** 1604, 1939

7 Friedman, B., and Prinzmetal, M. Vasomotor Effects of Blood in Patients with Hypertension and Animals with Experimental Hypertension, *Ann Int Med* **12** 1617, 1939

cipitation with ammonium sulfate, the pressor substance was found in the precipitate by Williams, Harrison and Mason⁸

Highly purified preparations of renin have been made by Helmer and Page⁹. They believe the substance to be a protein. Color tests for guanidine groups and for pentose were especially strong. The purest preparations were found to elevate the blood pressure of dogs 30 mm of mercury when given in amounts representing 0.027 mg of nitrogen per kilogram of body weight. In cats it was three times as active, since 0.009 mg per kilogram would produce the same rise in blood pressure as the larger dose in the dog. Swingle, Taylor, Collings and Hays¹⁰ describe a method of purifying renin by saline extraction and ammonium sulfate precipitation, no organic solvents being used. The substance is stable if frozen or dried by the lyophile process. They define a renin unit as the minimum amount necessary, when given intravenously over a period of two to five seconds, to raise the mean blood pressure of anesthetized dogs an average of 40 mm of mercury above the starting level. This unit is equivalent to 0.1 mg of solid material per kilogram of body weight. The effects observed were proportional to the dose, up to 3 mg per kilogram. Higher doses were found not to give proportionally greater effects. Renin was found to be non-toxic in doses up to 35 mg.

Atumi¹¹ describes a substance found in the blood of the renal veins which raises the blood pressure of normal rabbits and those having splanchnic sections. This substance is said to be soluble in ethyl alcohol, ether, chloroform and acetone. He believes it to be a sterol. Obviously this substance differs markedly from the renin just described.

As one might suppose, renin is being actively studied from the physiologic and pharmacologic standpoints. Page¹² and Merrill, Williams and Harrison¹³ agree in their reports that the pressor effect is elicited by direct action on the blood vessels, a conclusion also reached

8 Williams, J. R., Jr., Harrison, T. R., and Mason, M. F. Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, *Am J M Sc* **195** 339, 1938.

9 Helmer, O. M., and Page, I. H. Purification and Some Properties of Renin, *J Biol Chem* **127** 757, 1939.

10 Swingle, W. W., Taylor, A. B., Collings, W. D., and Hays, H. W. Preparation and Bioassay of Renin, *Am J Physiol* **127** 768, 1939.

11 Atumi, Y. Control of Blood Pressure by Nephrohormone, *J Chosen M A* **29** 326, 1939, abstracted, *Chem Abstr* **33** 5055, 1939.

12 Page, I. H. On the Nature of the Pressor Action of Renin, *J Exper Med* **70** 521, 1939.

13 Merrill, A., Williams, J. R., Jr., and Harrison, T. R. The Site of Action of the Renal Pressor Substance, *Am J M Sc* **196** 18, 1938.

by Tigerstedt, and that it is little influenced by elimination of the nervous system, the hypophysis, the adrenal glands, the pancreas, the liver or the kidneys. The latter investigators found the action of renin to be heightened if the kidneys are removed two or three days before injection. Fasciolo, Houssay and Taquini⁵ found that the presence of healthy kidneys is capable of diminishing the pressor effect of renin. They have also found that grafting an ischemic dog kidney into a dog from which both kidneys have been removed will elevate the blood pressure whether the adrenal glands have been removed or not, a result that is not in agreement with some earlier work. That some conflicting conclusions are reached by the various investigators who are studying renin is not surprising, since several methods of preparation are in use.

Page¹² has found that on giving successive injections of renin a diminishing pressor response is obtained. This fact was noted in Tigerstedt's original work. Page attributes this phenomenon to one or both of two causes, either to the progressive exhaustion of a renin activator or to the development of an antistubstance. In favor of the existence of a renin activator is the fact that no vasoconstrictor effect is observed when a rabbit's ear is perfused with pure renin dissolved in Ringer's solution. The activator is believed to be a protein-like substance present in normal blood, since the constrictive effect is obtained when a rabbit's ear is perfused with blood to which renin has been added. On successive additions of renin to this blood the renin activator appears to be exhausted. If the ear is perfused with fresh blood the constrictive response to the added renin is restored.

The effect of renin on the intrinsic circulation of the kidney itself has been studied by Merrill, Williams and Harrison¹⁵. These workers have been able to obtain two pressor substances from kidneys, one, renin, being obtained from the saline extract and the other, a tyramine-like substance, from autolysate. They found differences in the action of these two substances. When renin elevates the blood pressure, the kidney swells, the blood flow through it is decreased, and the volume of the urine is increased. This is interpreted as an indication that renin causes a constriction of the efferent arterioles of the glomerulus. On the other hand, tyramine was thought to constrict the afferent arterioles, since its action caused a shrinkage in volume of the kidneys and a diminution of renal blood flow.

¹⁴ Footnote deleted

¹⁵ Merrill, A., Williams, R. H., and Harrison, T. R. The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Rats and Dogs, *Am J M Sc* **196** 240, 1938

In a series of lectures given at the University of Kansas, Homer Smith¹⁶ reviews his observations on the mechanism controlling renal blood flow. He has found that under ordinary circumstances the flow is chiefly regulated by variations in the tonus of the efferent glomerular artery. When this artery is constricted the blood flow is diminished, when it dilates, the flow is increased. Constriction of this arteriole has the effect of raising the filtration pressure within the glomerulus so that even when the blood flow is thus diminished the amount of glomerular filtrate tends to remain constant. Agents capable of causing constriction of the afferent glomerular arteriole would also have the effect of diminishing the total blood flow through the kidney, but in this case the expected result would be a diminution in the amount of glomerular filtrate as well. Smith believes that the control of the tonus of the efferent arteriole is independent of the connections of the kidney with the nervous system, hence a great measure of constancy of renal function may be achieved during wide variations in systemic blood pressure and blood flow, though it is obvious that extreme variations in the latter factors must have effects on the afferent blood supply to the kidney for which no intrinsic compensation could be made. Reference will be made subsequently to the application of this work to the study of hypertension in human subjects.

Corcoran and Page¹⁷ observed that the slow intravenous infusion of renin elevated blood pressure, constricted the efferent glomerular arterioles and diminished renal blood flow, findings which are in agreement with those of others¹⁵. In contrast, similar infusion of pitressin produced variable effects on the renal blood flow and no effect on the systemic blood pressure.

The influence of sympathomimetic substances has received the attention of several investigators, with divergent results. Williams¹⁸ found that the pressor effects of renin were enhanced by cocaine and inhibited by

16 (a) Smith, H. W. *Studies in the Physiology of the Kidney. I. Newer Methods of Study of Renal Function in Man, III. The Renal Blood Flow in Normal and Hypertensive Subjects*, Publication of the University Extension Division, University of Kansas, Lawrence, Kan., 1939, (b) *New Aspects of Renal Physiology*, *J. Urol.* **41**: 867, 1939. (c) Smith, H. W., Rovenstine, E. A., Goldring, W., Chassis, H., and Ranges, H. A. *The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation*, *J. Clin. Investigation* **18**: 319, 1939.

17 Corcoran, A. C., and Page, I. H. *The Effects of Renin and Pitressin and Atropine on Renal Blood Flow and Clearance*, *Am. J. Physiol.* **126**: 354, 1939.

18 Williams, J. R., Jr. *The Effect of Cocaine and Ergotamine on the Action of the Renal Pressor Substance*, *Am. J. Physiol.* **124**: 83, 1938.

ergotamine. On the other hand, Katz and Friedberg¹⁹ found that the quantitatively similar pressor action of renin in normal and in hypertensive dogs is not abolished by piperidomethylbenzodioxane, a substance which reverses the action of epinephrine in dogs and resembles the action of ergotamine in this respect. From this he concluded that renin does not act as a sympathomimetic substance.

The influence of various ductless glands on the action of renin is still somewhat confused. Fasciolo, Houssay and Taquini⁵ noted that hypophysectomy diminished the blood pressure of dogs with renal ischemia. They observed that renin exerted its pressor effects in the absence of the adrenal glands. A small remnant of adrenal tissue will keep the blood pressure high in hypertensive dogs. Williams, Diaz, Burch and Harrison²⁰ found that rats which were kept alive after adrenalectomy by having salt administered to them were less sensitive to the action of renin, although their kidneys on assay did not contain less renin than the kidneys of normal rats. Rats after hypophysectomy were more sensitive to renin, their kidneys likewise yielding normal amounts of renin. Castriation was found to have no effect on sensitivity to renin nor on the renin content of the kidneys.

Grossman and Williams²¹ have studied the effect of age on the sensitivity to renin. Doses were given to rats of various ages in proportion to the body surface. Young rats, aged 6 to 10 weeks, showed the least rise in blood pressure, while the oldest rats, 2½ years of age, exhibited the greatest rise. The authors suggest that this effect of age on sensitivity to the action of renin may be one of the factors involved in the greater frequency of hypertension in old age.

EXPERIMENTAL URETERAL OBSTRUCTION

The effects of ureteral obstruction on the blood pressure have been receiving renewed attention. Blalock and Levy²² credit Rautenberg, in 1910, with having been the first to observe hypertension following experimental ligation of the ureters. Harrison, Mason, Resnik and

19 Katz, L. N., and Friedberg, L. The Hemodynamic Effect of the Dioxane Derivative 933F on Trained Unanesthetized Normal and Renal Hypertensive Dogs and Its Effect on the Pressor Action of Renin, *Am J Physiol* **127**:29, 1939.

20 Williams, J. R., Jr., Diaz, J. T., Burch, J. C., and Harrison, T. R. The Relation of the Adrenal Glands to the Action of the Renal Pressor Substance, *Am J M Sc* **198** 212, 1939.

21 Grossman, E. B., and Williams, J. R., Jr. Relation of Age to Renal Pressor Substance, *Arch Int Med* **62** 799 (Nov) 1938.

22 Blalock, A., and Levy, S. E. Studies on the Etiology of Renal Hypertension, *Ann Surg* **106** 826, 1937.

Raney²³ have made similar observations. Pickering and Prinzmetal²⁴ did not observe hypertension following unilateral ligation of the ureters in 4 rabbits. Williams, Wegria and Harrison²⁵ found that unilateral ligation sometimes did and sometimes did not elevate the blood pressure. Even when no hypertension followed unilateral ligation, the sensitivity to renin was increased. When hypertension was induced by unilateral ligation of the ureter, Blalock and Levy²² were able to abolish it by removal of the hydronephrotic kidney. Rats with bilateral spontaneous hydronephrosis were found²⁵ regularly to exhibit hypertension, and such rats showed a much more pronounced pressor response to renin than did rats without hydronephrosis. These observations may have some bearing on the observations of Dill and Erickson,²⁶ who noted that slight renal ischemia, which was followed by no severe disturbance in nonpregnant dogs, caused fulminating eclampsia in pregnant dogs. Whether the physiologic hydronephrosis of pregnancy had an effect of increasing the sensitivity to renin has not been determined. There are of course, many other possible reasons which might be advanced in explanation of the eclampsia observed.

SECONDARY PHENOMENA IN EXPERIMENTAL HYPERTENSION

Gibson and Robinson²⁷ have observed the blood volume in dogs with hypertension induced by Goldblatt clamps on the renal arteries. Cardiac hypertrophy developed in all the animals. No constant trend of the blood volume was observed in these animals. Renal function was unimpaired. One dog with congestive heart failure was found to have an increase in blood volume.

It has long been thought that arteriolar sclerosis is a result rather than a cause of hypertension. The microscopic appearances of arte-

23 Harrison, T. R., Mason, M. F., Resnik, H., and Raney, J. Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, *Tr. A. Am. Physicians* **51** 280, 1936.

24 Pickering, G. W., and Prinzmetal, M. Experimental Hypertension of Renal Origin in the Rabbit, *Clin. Sc.* **3** 357, 1938.

25 Williams, J. R., Jr., Wegria, R., and Harrison, T. R. Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, *Arch. Int. Med.* **62** 805 (Oct.) 1938.

26 (a) Dill, L. V., and Erickson, C. C. Eclampsia-Like Syndrome Occurring in Pregnant Dogs and Rabbits Following Renal Artery Constriction, *Proc. Soc. Exper. Biol. & Med.* **39** 362, 1938. (b) Dill, L. V., Isenborn, C. E., and Cadden, J. F. The Effect of Quantitative Reduction of Renal Blood Flow upon the Pregnant Rabbit, *J. Clin. Investigation* **18** 641, 1939.

27 Gibson, J. G., and Robinson, R. W. Blood Volume, Cardiac Size and Renal Function in Dogs with Hypertension Produced by the Goldblatt Technique, *Proc. Soc. Exper. Biol. & Med.* **39** 497, 1938.

arteriolar lesions in "benign" hypertension have been contrasted with those occurring in "malignant" hypertension. Acute arteriolar lesions of the "malignant" variety have been found by Wilson and Pickering²⁸ in rabbits with experimental hypertension induced by partial constriction of the renal arteries. The incidence of these lesions is related to the degree of hypertension rather than to its duration. They were observed most frequently in the arterioles of the intestine, stomach, liver, adrenal glands, heart and eyes. The arterioles of the ischemic kidneys did not undergo these changes. In this respect the intrinsic circulation of the experimental animals employed (rabbits) differs from that commonly found in human subjects with "malignant" hypertension.

"ESSENTIAL" HYPERTENSION

Under the impact of the rapid accumulation of new facts regarding renal hypertension, the conception of "essential" hypertension is, of necessity, undergoing profound alterations. In the last review^{28a} it was noted that clinical and pathologic reports were accumulating in illustration of the manner in which the condition of renal ischemia occurred in man. Further evidence is now available as to the importance of lesions affecting the patency of the large renal arteries. Blackman²⁹ reports the pathologic changes in 50 cases of "essential" hypertension as compared with the changes in a control series of 50 nonhypertensive subjects, balanced as to the incidence of age and sex. He found that in 86 per cent of the cases of hypertension the patients showed narrowing of the main renal arteries at or near the aorta. In 54 per cent the narrowing was pronounced, and in 32 per cent the lumen was narrowed to 1.5 mm or less. In 14 per cent no significant narrowing was observed. In only 10 per cent of the controls was any narrowing of the renal arteries discovered. Leadbetter and Burkland³⁰ report the interesting case of a Negro boy 5½ years of age who had suffered from marked hypertension for three years. Operative removal of an ectopic kidney, the main renal artery of which was nearly occluded by a smooth muscle tumor, led to relief of the hypertension. Boyd and Lewis,³¹ in the course

28 Wilson, C, and Pickering, G W. Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, *Clin Sc* **3** 343, 1938.

28a McCann, W S. Bright's Disease. A Review of Recent Literature, *Arch Int Med* **63** 590 (March) 1939.

29 Blackman, S S. Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, *Bull Johns Hopkins Hosp* **65** 353, 1939.

30 Leadbetter, W F, and Burkland, C E. Hypertension in Unilateral Renal Disease, *J Urol* **39** 611, 1938.

31 Boyd, C H, and Lewis, L G. Nephrectomy for Arterial Hypertension, *J Urol* **39** 627, 1938.

of bilateral exploration for an adrenal tumor, found a kidney in which there was a large infarct and marked arterial disease. The patient, a man of 31 years, had persistent elevation of blood pressure. Removal of the kidney was followed by a return of the blood pressure to normal range. Changes in the eyegrounds noted at the time of operation did not regress as the blood pressure fell. Blatt and Page³² report finding a patient with hypertension whose renal arteries were constricted by a retroperitoneal tumor.

It has long been known to urologists that urinary obstruction is frequently associated with hypertension and that relief of the obstruction is commonly followed by lower blood pressure. An interesting study bearing on this point was made by Maher and Wosika,³³ who reviewed the records of 600 patients with hypertension. Of these, about one fifth had abnormalities of the urinary tract and kidneys, four fifths being left in the category of persons with "essential" hypertension. In the cases of urologic involvement with elevated blood pressure, prostatic hypertrophy was most frequent and chronic pyelonephritis next in frequency. The authors give a long list of other conditions in which various combinations of urolithiasis, obstruction and infection were present. Schroeder and Steele³⁴ made a study of "essential" hypertension in 71 young subjects who revealed no functional impairment of the kidneys. Intravenous pyelograms revealed abnormalities in 50 of the 71 patients. About one half of their patients had some form of urinary obstruction. In our clinic my associates and I have been greatly impressed with the frequency with which unsuspected obstruction and asymptomatic pyelonephritis are discovered in cases thought to be instances of "essential" hypertension. A report of these observations is in press.³⁵

The complexity of the problem of trying to untangle the clues to the etiology of the disorders formerly grouped under the diagnosis of "essential" hypertension is well illustrated by the efforts of Schroeder and Steele³⁶ to classify 218 cases according to the clinical conditions associated with the hypertension. Five groups were made according to the predominant condition. In the renal group were 56 cases, with

32 Blatt, E, and Page, I. H. Hypertension and Constriction of the Renal Arteries in Man. Report of a Case, *Ann Int Med* **12** 1690, 1939.

33 Maher, C. C., and Wosika, P. H. Urologic Hypertension. A Study of One Hundred and One Cases, *J Urol* **41** 893, 1939.

34 Schroeder, H. A., and Steele, J. M. Abnormalities in the Urinary Tract in "Essential Hypertension," *Proc Soc Exper Biol & Med* **39** 107, 1938.

35 McCann, W. S. Chronic Pyelonephritis. A Cause of Hypertension and Renal Insufficiency, *New York State J Med*, to be published.

36 Schroeder, H. A., and Steele, J. M. Studies on "Essential" Hypertension I. Classification, *Arch Int Med* **64** 927 (Nov) 1939.

14 cases of glomerulonephritis, 8 of calculus and 4 of pyelonephritis. In 29 cases there were the factors of stone, infection or obstruction, either alone or in combination. In 3 cases pregnancy was a factor. Similarly, in the other groupings, of nervous, endocrine, vascular and unclassified disorders, pregnancy appeared as a factor. A similar study has been made by Williams and Harrison,³⁷ with comparable results. It is obvious at this time that the term "essential hypertension" does not apply to any clinical entity. In view of the rapid progress of knowledge it will probably soon fall into entire disuse. At present it seems probable that in 80 to 85 per cent of these cases the condition depends on atheromatous narrowing of the larger renal arteries at or near the aorta and that in 15 to 20 per cent the trouble is due to unsuspected disorders of the kidneys or the urinary passages.

PYELONEPHRITIS

In previous reviews the growing interest in this subject has been recorded, in particular its relationship to hypertension and to the toxemias of pregnancy. The subject is thoroughly reviewed by Weiss and Parker,³⁸ with an extensive bibliography and a careful analysis of 100 cases. These authors confirm the original thesis of Wilson and Schloss, that pyelitis never exists without pyelonephritis. The extreme variability of the clinical course is emphasized. The infection may heal in a short time, or it may persist in a chronic form with either continuous or intermittent activity of the infection. The description of the morphologic changes observed in the kidneys of 100 patients is most complete and emphasizes several points, namely, the involvement of the lymphatic system of the kidneys and the variety of vascular changes observed. It is particularly noteworthy that in unilateral pyelonephritis the vascular lesions may be confined to the affected side. With such unilateral involvement hypertension may or may not be observed. The vascular lesions are similar to the severe obliterative lesions found in malignant nephrosclerosis. Weiss and Parker estimate that in 15 to 20 per cent of the cases "malignant" hypertension is due to pyelonephritis.

Encephalopathy, neuroretinitis and left ventricular failure with cardiac asthma were frequently observed in cases of hypertension due to pyelonephritis. However, organic diseases of the cerebral and coronary vessels appear to have occurred less frequently than in hypertensions of other origin. The vascular lesions of chronic pyelonephritis

37 Williams, J. R., Jr., and Harrison, T. R. Clinical Pictures Associated with Increased Blood Pressure. A Study of One Hundred Patients, *Ann Int Med* **13** 650, 1939.

38 Weiss, S., and Parker, F., Jr. Pyelonephritis. Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18** 221, 1939.

were found to be mainly restricted to the kidneys, in contrast to those of "primary" malignant hypertension, which are generalized

Pyelonephritis was found rarely to coexist with glomerulonephritis. In pyelonephritis glomerular changes are observed, but these may be distinguished from those occurring in glomerulonephritis. The chronic and healed forms of the disease are more frequent than glomerulonephritis.

Pyelonephritis may complicate polycystic kidneys, hydronephrosis and tuberculosis of the kidneys. The vascular lesions characteristic of pyelonephritis did not occur in tuberculosis of the kidneys or in hydronephrosis which was uncomplicated by it.

Weiss and Parker believe that the hypertension of pyelonephritis is due to renal ischemia. This belief is presumably based on the character of the vascular lesions induced by this type of inflammatory process in the kidneys and the constrictive character of the interstitial fibrosis leading to contraction of the kidney. These authors emphasize the implications of the knowledge of this condition in the practice of preventive medicine. Since pyelonephritis is the one form of renal disease that can be successfully treated in its initial stages, a charge is laid on the conscience of every physician who encounters it to nip it in the bud so that its disastrous sequelae may be avoided.

GLOMERULONEPHRITIS

The experimental production of glomerulonephritis by means of nephrotoxic serums of heterologous origin has provided no explanation of the pathogenesis of the disease as it occurs in man. Some recent observations of Schwentker and Comploier³⁹ are illuminating in this respect. Rabbits were given injections of emulsions of homologous kidneys, alone and in combination with streptococcus toxin or staphylococcus toxin. There were also controls which received the toxins alone. In the blood of rabbits which had received injections of both the kidney emulsion and one or the other toxin, complement-fixing antibodies were found, one specific for kidney tissue and one nonspecific, in that it could be absorbed by the brain. Similar complement fixations were obtained with the blood of a majority of patients with scarlet fever. In only a few instances did the blood of normal patients exhibit this phenomenon. This work suggests that cytotoxins originate autogenously when the kidney is injured by toxins. It does not explain, however, why it is that in some persons clinically recognizable nephritis develops after scarlet fever while it does not develop in others.

³⁹ Schwentker, F. F., and Comploier, F. C. The Production of Kidney Antibodies by Injection of Homologous Kidney Plus Bacterial Toxins, *J. Exper. Med.* **70** 223, 1939.

Concerning the optimal amount of protein to be given in the diet of patients with glomerulonephritis, there has been considerable divergence of opinion. In recent years the trend of opinion in clinical circles has been definitely in favor of greater liberality, with some dissenting voices. Cameron⁴⁰ has reviewed the evidence in favor of a liberal ration of protein. From his own experience he recommends only temporary and moderate restriction during the initial and terminal stages. Under other circumstances he advocated a basic ration of 70 to 80 Gm per day, to which should be added the equivalent of the protein lost in the urine.

There have come from experimental laboratories certain observations which call for careful consideration and evaluation by clinicians. Smadel and Farr⁴¹ have observed the effect of the amount of protein in the diet on the course of experimental nephrotoxic nephritis in rats. These rats were divided into groups receiving low, medium and high protein diets (4, 14 and 32 per cent of the total number of calories, respectively). In those rats of the Whelan strain receiving low protein diets there was clinical and pathologic evidence that the disease subsided rapidly. The acute tubular injury resolved without permanent damage, and only moderate residual changes were noted in the glomeruli. In contrast, the disease progressed rapidly to renal failure in those receiving high protein diets. In more than half of the rats receiving medium protein diets renal failure developed, the general results being similar to those obtained in rats on a mixed stock diet.

One of the most significant effects observed in rats receiving the high protein diets is obliterative scarring of the tubules, with general evidence of epithelial injury of the kidneys. The diets given were isocaloric, the low protein diets being high in carbohydrate and the high protein diets low in carbohydrate. The question therefore rises in my mind as to whether or not the tubular injury may have been due rather to the lack of the protective action of carbohydrate against toxic injury, an action analogous to that exerted by carbohydrate in the liver. This would explain one discrepancy between these findings and the clinical observations made by my associates and me in our clinic, since the diets given there, which seemed not to exert any harmful effect, were liberal in the use of carbohydrate as well as of protein.⁴²

40 Cameron, J. D. S. Protein in the Treatment of Nephritis, *Edinburgh M. J.* **46** 386, 1939.

41 Smadel, J. E., and Farr, L. E. The Effect of Diet on the Pathological Changes in Rats with Nephrotoxic Nephritis, *Am. J. Path.* **15** 199, 1939. Farr, L. E., and Smadel, J. E. The Effect of Dietary Protein on the Course of Nephrotoxic Nephritis in Rats, *J. Exper. Med.* **70** 615, 1939.

42 McCann, W. S. The Many Sided Question of Protein in Nephritis, *Ann. Int. Med.* **5** 579, 1931. Keutmann, E. H., and McCann, W. S. Dietary Protein in Hemorrhagic Bright's Disease, *J. Clin. Investigation* **9** 973, 1932.

In a later paper Smadel and Swift⁴³ note the fact that the Whelan strain and the Evans strain of rats react differently as to the effect of the nephrotoxic serum and diet. In the latter rats the nephritis tended to subside rapidly and independently of the character of the diet. The greater susceptibility to the deleterious effects of protein may be a peculiarity of the Whelan strain.

Further light is thrown on this question of the dietary protein by Addis and Lew⁴⁴ and Bergman and Drury,⁴⁵ who have arrived independently at the same conclusion, namely, that the deleterious effect of meat protein is due to the high content of potassium. The former investigators produced anuria and a great increase in blood urea by ligation of the vena cava just above the point of entry of the renal veins. In groups of 40, rats were given diets designed to induce wide variations in protein consumption and catabolism. None of the animals died when given diets which were low in protein or which included moderate amounts of milk and cereal protein. With diets of dried yeast and casein no deaths occurred. When the intake of protein was large, including dried liver, kidney and beef, the mortality of the groups of rats was 8, 9 and 16 per cent, respectively. A water extract of the meat gave a 52 per cent mortality, while an alcohol-soluble extract gave none. Solutions of potassium acid phosphate (KH_2PO_4) and chloride caused the same mortality rate among the rats as did the water extract.

Bergman and Drury observed that the survival time after bilateral nephrectomy could be made very uniform under standard conditions. If sugar was given to the rats the survival was prolonged. If meat was given it was shortened. The urine of meat-fed rats was deleterious, and this effect was believed to be due to the high potassium content of this urine.

If the foregoing observations and interpretations are correct, the amount of protein may prove to be not as important as its source. Milk proteins may be less objectionable from the standpoint of having less potassium. One may also speculate as to whether the toxic effects of potassium might not be removed if there were a proper balance of other mineral substances, such as calcium and sodium. These questions are not answered in the studies just referred to.

43 Smadel, J. E., and Swift, H. F. The Effect of Prolonged Administration of Sulfanilamide on Rats with Nephrotoxic Nephritis, *J. Clin. Investigation* **18** 757, 1939.

44 Addis, T., and Lew, W. Diet and Death in Acute Uremia, *J. Clin. Investigation* **18** 773, 1939.

45 Bergman, H. C., and Drury, D. R. A Study of Acute Renal Insufficiency. *J. Clin. Investigation* **18** 777, 1939.

A series of papers by Chanutin and Ludewig⁴⁶ appear to have somewhat the same import as those of Beigman and Diury, except that the deleterious effects were not attributed to potassium

The nature of the arteriolar tonicity in acute glomerulonephritis has been studied by Arnott and Matthew,⁴⁷ the heat elimination from one hand being used as a measure of the blood flow through the hand. When the other hand was immersed in cold water the elimination of heat of the immersed hand was greater than normal, and this was taken as an indication of an increased blood flow. These observations were in confirmation of some previous work by Pickering, who found the blood flow normal in chronic hypertension and increased in acute hypertension under the conditions described. These observations recall the work of Landis, Montgomery and Spickman, which has been previously reviewed, their work showed that the action of renin is unlike that of other pressor substances in that it does not decrease the temperature of the skin.

The hypertension of glomerulonephritis has been shown by Hayman, Martin and Miller⁴⁸ to bear little relationship to the number of patent glomeruli. For a number of years Hayman has employed a method of estimating the number of glomeruli remaining patent. In the most recent study it was found that when less than 700,000 glomeruli per kidney were patent the systolic blood pressure was 150 or more. Below this critical level there was no correlation with the count of glomeruli, and elevation of blood pressure was observed in instances in which there was little or no reduction in the count. However, if the maximum concentration of the urine is considered, one again finds a critical decrease in concentrating power at about 700,000 glomeruli per kidney. Below that level the maximum specific gravity is 1.010. When hypertension occurs in glomerulonephritis, together with low concentrating power, one may suppose that the number of patent glomeruli are less than 700,000 per kidney, and if the maximum concentration is in normal limits, more than this number of glomeruli are patent. Hayman points

46 Chanutin, A., and Ludewig, S. Experimental Renal Insufficiency Produced by Partial Nephrectomy. XI Diets Containing Dried Extracted Liver, *Arch Int Med* **64**:513 (Sept) 1939, XII Diets Containing Dried Extracted Meat, *ibid* **64** 526 (Sept) 1939, XIII A Summary of the Effect of Whole Liver, Whole Meat, Extracted Liver and Extracted Meat Diets on Renal Hypertrophy, Renal Function, Blood Pressure, and Cardiac Hypertrophy, *ibid* **64** 747 (Oct) 1939, XIV Diets Containing Whole Dried Yeast, *ibid* **64** 756 (Oct) 1939.

47 Arnott, W. M., and Matthew, G. D. The Nature of the Arteriolar Hypertonicity in Acute Glomerulo-Nephritis, *Quart J Med* **8**:353, 1939.

48 Hayman, J. M., Jr., Martin, J. W., Jr., and Miller, M. Renal Function and the Number of Glomeruli in the Human Kidney, *Arch Int Med* **64** 69 (July) 1939.

out that the degree of functional impairment in the glomeruli may be greater than the degree of damage revealed in the histologic preparations. It was found that in certain cases of acute infections and jaundice clearance and concentrating ability may be markedly reduced in spite of a normal number of glomeruli showing no significant change in the histologic sections.

INTERCAPILLARY GLOMERULOSCLEROSIS

In 1936 a syndrome was described by Kimmelstiel and Wilson,⁴⁹ consisting of diabetes, albuminuria, hypertension, retinal vascular changes and a nephrotic syndrome, and some degree of renal insufficiency was found to be associated with a peculiar intercapillary glomerulosclerosis. A number of cases of this syndrome have been collected and are further described by Newburger and Peters.⁵⁰ In the glomeruli, hyaline deposits are laid down between the basement membrane and the epithelium. Amyloid is to be excluded. The picture is not to be confused with intercapillary fibrosis, which sometimes occurs in glomerulonephritis and may be recognized by special stains of the basement membrane. The authors regard the condition as a clinical entity which depends on severe and extensive arterial and arteriolar degeneration associated with and perhaps resulting in diabetes and renal damage.

THE NEPHROSES

Support for the idea that there is a genuine lipid nephrosis, as distinguished from a nephrotic stage of glomerulonephritis, is strongest in pediatric circles. Bearing on a peculiar metabolic disturbance in the nephroses of children are some important observations of Farr.⁵¹ He observed that the nitrogen balance of 2 children with the nephrotic syndrome showed marked spontaneous changes which preceded clinical evidences of increased severity of the syndrome. Mild infections of the upper respiratory tract tend to produce negative nitrogen balances, with failure to assimilate nitrogen and increased proteinuria. Nephrotic crises occur which are not uniformly accompanied by an increase in nitrogen loss. Such episodes reflect an acute disturbance in a patient chronically manifesting evidence of inability to assimilate protein.

49 Kimmelstiel, P., and Wilson, C. Intercapillary Lesions in the Glomeruli of the Kidney, *Am J Path* **12** 83, 1936.

50 Newburger, R. A., and Peters, J. P. Intercapillary Glomerulo-Sclerosis. A Syndrome of Diabetes, Hypertension, and Albuminuria, *Arch Int Med* **64** 1252 (Dec.) 1939.

51 Farr, L. E. Assimilation of Protein by Young Children with Nephrotic Syndrome. III. Effect of Nephrotic Crises on Assimilation of Nitrogen, *Am J Dis Child* **58** 939 (Nov.) 1939.

Farr⁵² also notes that when these children are on a fixed nitrogen intake varying the proportions of fat and carbohydrate has no effect on the nitrogen balance.

In the nephroses of children Farr and Van Slyke⁵³ find that edema can be controlled satisfactorily in most instances by simple restriction of salt, together with an adequate diet, when the plasma albumin concentration is above 1.2 Gm per hundred cubic centimeters. This concentration is decidedly below that of 2.5 Gm per hundred cubic centimeters found for adults in their clinic.

MacLeod and Farr⁵⁴ discuss the unusual susceptibility of nephrotic children to pneumococcal peritonitis. The attacks of this infection are usually due not to freshly acquired organisms but to an organism carried for some time, which invades when the resistance is lowered by some metabolic disturbance, such as the acute nephrotic crises previously described.

The observations of Major⁵⁵ on the treatment of lipoid nephrosis show that the best results were obtained by the use of high carbohydrate diets, blood transfusions and diuretics. Administration of an anterior pituitary extract (antuitrin G), choline (hydroxyethyltrimethylammonium hydroxide) and adrenal cortex extract had no appreciable effect on the course of the disease, although in some instances the ingestion of choline seemed to lower the content of blood cholesterol.

Yuile and Knutti⁵⁶ report experiments on the use of acacia which should further discourage those who would rashly use this substance in the management of the edema of nephrosis. When weekly intravenous injections of acacia were repeated for four or five months, it was found possible to maintain the concentration of plasma protein and of total circulating protein at a low level. When the injections were stopped the effect continued for several months more, during which the acacia remained in the blood. That the fibrinogen of the plasma was reduced out of proportion to the other proteins indicated an effect on the liver. Plasma volume decreased at first and then

52 Farr, L. E. Assimilation of Protein by Young Children with Nephrotic Syndrome, *Am J Dis Child* **58** 935 (Nov.) 1939.

53 Farr, L. E., and Van Slyke, D. D. Relation Between Plasma Protein Level and Edema in Nephrotic Children, *Am J Dis Child* **57** 306 (Feb.) 1939.

54 MacLeod, C. M., and Farr, L. E. Relation of the Carrier State to Pneumococcal Peritonitis in Young Children with Nephrotic Syndrome, *Proc Soc Exper Biol & Med* **37** 556, 1937.

55 Major, R. H. Observations on the Treatment of Lipoid Nephrosis, *Ann Int Med* **12** 1555, 1939.

56 Yuile, C. L., and Knutti, R. Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia. II. Production of Chronic Hypoproteinemia. *J Exper Med* **70** 605, 1939.

increased to a value 20 to 24 per cent above basal levels, but the total blood volume did not increase since there was a decrease in cell volume. These observations appear to me as highly important, since they indicate that the injection of acacia may actually interfere with the regeneration of plasma protein through interference with hepatic function.

The early recognition of renal amyloidosis in tuberculous patients is discussed by Altnow, Van Winkle and Cohen⁵⁷. In a majority of the cases studied the onset could be dated with reasonable accuracy from some clinical event, such as the onset of enteritis, pleural effusion, empyema, or other suppuration, the institution of pneumothorax or some other surgical procedure. In the greater number of patients amyloidosis developed in association with enteritis, or in association with pleuritis, peritonitis or pericarditis, alone or in combination. If the diagnosis were to be made only on the observation of suppurative lesions in association with enlargement of the liver and spleen, the great majority of the cases would be missed. Hyposthenuria was the most constant single finding.

Concerning renal disease in syphilis Baker⁵⁸ makes an interesting report. It appears that there is a not infrequent type of nephrotic lesion to be observed in the kidneys of those dying with syphilis. This has been described by Rich and also by Bauer. Occasionally this condition may be manifest as a clinical nephrosis, and in cases of this type as well as in those of hemorrhagic nephritis occurring in syphilitic patients, lesions may heal under antisyphilitic therapy. In the cases of hemorrhagic nephritis healing may be produced by the closing over of ulcers of the upper respiratory tract, through which infection may have entered to give rise to the nephritis. There remains the possibility that the spirochetes may be capable of exciting either a nephrosis or a nephritis. The effect of therapy is suggestive but not conclusive.

Smetana⁵⁹ describes the clinical events and the pathologic changes occurring in patients in whom a nephrosis develops after the inhalation of carbon tetrachloride. In addition to hepatic damage the renal symptoms consist of oliguria or anuria, azotemia and subsequent hypertension and the presence in the urine of albumin, leukocytes, red cells, casts and bile. Histologically, the kidneys reveal a distention of Bowman's capsule by an albuminous precipitate and swelling of the

57 Altnow, H. O., Van Winkle, C. C., and Cohen, S. S. Renal Amyloidosis. A Further Study of the Clinical Course and Pathological Lesions in Fifty-Seven Cases, *Arch. Int. Med.* **63**: 249 (Feb.) 1939.

58 Baker, B. M., Jr. The Relation of Syphilis to Nephritis, *Bull. Johns Hopkins Hosp.* **65**: 196, 1939.

59 Smetana, H. Nephrosis Due to Carbon Tetrachloride, *Arch. Int. Med.* **63**: 760 (April) 1939.

lining cells, by swelling and vacuolation of the proximal tubular epithelium and by degeneration and necrosis of the distal tubular cells and Henle's loop, with desquamation and plugging of the tubules. Concretions are present, the nature of which remains obscure.

Much has been written about the renal complications of multiple myeloma. Some recent observations of Ulrich⁶⁰ indicate that in some cases hydronephrosis occurs as a result of obstruction of the tubules by casts of Bence-Jones protein. In other cases the mechanism is not known.

PHYSIOLOGIC STUDIES

Homer Smith and his collaborators⁶¹ have extended their studies of the renal circulation to determine the effects of high spinal anesthesia. When this is carried to levels considerably above those at which the sympathetic pathways to the kidneys emerge from the cord, renal hyperemia was not observed, nor was there any consistent effect on the renal circulation. This confirmed their view that the tonus of the renal arterioles is normally maintained by the autonomous intrinsic activity of the peripheral vascular apparatus and that it is not dependent on the activity of the central nervous system.

In work previously reviewed, Smith and his colleagues estimated that the normal renal blood flow as measured by the diodrast clearance is in the neighborhood of 1,340 cc per minute for a man of 1.73 square meters of body surface. Chesley and Chesley⁶² present data which indicate that the estimates arrived at by Smith are too high. In a group of normal women they found the renal blood flow to be 879 cc per minute, the flow being 856 cc in a group of pregnant women. They suggest that the higher result obtained by Smith was due to the fact that the diodrast was given in the same infusion with inulin, phenol-sulfonphthalein and sometimes sodium sulfate. They point out that Herrick, Mann and Sheehan⁶³ found that phenolsulfonphthalein and creatinine alter the renal blood flow as measured by a thermostohmuhr.

Chesley and Chesley also calculate that the renal blood flow of other animals is 3.2 to 3.3 cc per gram of kidney. Estimating the average

60 Ulrich, H. Multiple Myeloma, *Arch Int Med* **64** 994 (Nov) 1939.

61 Smith, H. W., Rovenstine, E. A., Goldring, W., Chassis, H., and Ranges, H. A. The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation, *J Clin Investigation* **18** 319, 1939.

62 Chesley, L. C., and Chesley, E. R. The Diodrast Clearance and Renal Blood Flow in Normal, Pregnant and Non-Pregnant Women, *Am J Physiol* **127**:731, 1939.

63 Herrick, J. F., Mann, F. C., and Sheehan, H. L. The Influence of Phenol Red and Creatinine on the Renal Blood Flow, *J Pharmacol & Exper Therap* **66** 73, 1939.

weight of the kidney in women studied, they believe that their results are more in keeping with this figure than are those of Smith. On the basis of mean kidney weight they would expect a total renal blood flow of 1,080 cc in men.

Chesley also comments on the variability of the proteinuria in the hypertensive toxemias of pregnancy.⁶⁴ The concentration of protein in the filtrate is calculated from that of the urinary protein by assuming it to be proportional to the ratio of the urinary creatinine to the endogenous creatinine. He found that the amount of protein filtered varies little from hour to hour in nephritic patients, in contrast to a great variability in women with toxemia, which he takes as an indication that the proteinuria is due to vascular spasm in such cases. It would seem unwise to accept this work without some reservations, especially in view of the possibility that some of the urinary protein may come from the tubules, just as some of the creatinine has been found to be secreted rather than filtered.

The blood volume in Bright's disease has been measured by Harris and Gibson.⁶⁵ The plasma volume was found to vary directly as the albumin and nonprotein nitrogen concentrations of the serum, and to vary inversely as the degree of anemia. The interrelation of the plasma and red cell volumes was such that the total blood volume was below normal in all stages of the disease. When congestive heart failure was present the volume was greater than it would have been without it. The circulation time was also observed to be prolonged in the nephrotic syndrome.

Smith^{16a} estimates that the normal tubules have the capacity of resorbing dextrose to a maximum capacity of 320 mg per minute and he points out that the renal threshold is to be conceived in terms of maximal resorptive capacity rather than in terms of plasma dextrose concentration. Govaerts and Muller⁶⁶ have studied the mechanism of dextrose excretion by the kidney in the diabetic dog. They take the creatinine clearance as the measure of the glomerular filtration and estimate the concentration of dextrose in the filtrate from the arterial plasma. In this way they estimate the amount of dextrose filtered per minute. As the value of blood sugar rises, the amount of dextrose resorbed increases to a maximum above which it does not increase no

64 Cheslev, L. C. The Variability of Proteinuria in the Hypertensive Complications of Pregnancy, *J Clin Investigation* **18** 617, 1939.

65 Harris, A. W., and Gibson, J. G., Jr. Clinical Studies of Blood Volume. VII. Changes in Blood Volume in Bright's Disease With or Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, *J Clin Investigation* **18** 527, 1939.

66 Govaerts, P., and Muller, P. The Mechanism of Glucose Excretion by the Kidney in Diabetic Dogs, *J Clin Investigation* **18** 25, 1939.

matter how high the value of the blood sugar. In 1 dog the threshold was thus found to be 390 mg, and in another, 347 mg. Similar studies were carried out in a case of diabetic coma reported by McCance and Widdowson⁶⁷. The urine contained only 13 mg of dextrose when the plasma sugar was 550 mg per hundred cubic centimeters, and the insulin clearance (filtrate) was 125 cc per minute. This would indicate a "threshold" or resorption of 670 cc per minute, a value greatly in excess of normal.

The effect of the adrenal glands on the excretion of sodium and potassium has been investigated by Harrison and Darrow⁶⁸. They found that after adrenalectomy the tubules failed to resorb sodium when the plasma sodium concentration was low and that they failed to excrete potassium when the plasma concentration of this substance was high.

In patients with essential and malignant hypertension de Wesselow and Thomson⁶⁹ found the serum potassium concentration to be lower than in normal persons on the same diet, and it was lower in persons with malignant hypertension than in persons with benign hypertension. Low levels of plasma sodium were not infrequently observed in patients with malignant hypertension. The administration of sodium salts was found to raise the blood pressure in patients with hypertension, while potassium salts were found to have the opposite effect. These alterations are slight and require amounts beyond the ordinary range found in the diet. Attempts to deplete the sodium content of the body were without effect.

MISCELLANEOUS

Lindberg, Wald and Barker⁷⁰ have found that the intravenous use of concentrated solutions containing 50 per cent of sucrose may produce transient reversible changes in the tubules and glomeruli of dogs. If the injections are often repeated the changes are more marked and may require a longer time for restitution or may even result in permanent alterations. No such changes occurred after similar use of 50 per cent solutions of d-sorbitol, 50 per cent solutions of dextrose or 10 per cent solutions of sodium chloride.

67 McCance, R. A., and Widdowson, E. M. Functional Disorganization of the Kidney in Disease, *J. Physiol.* **95** 36, 1939.

68 Harrison, H. E., and Darrow, D. C. Renal Function in Experimental Adrenal Insufficiency, *Am. J. Physiol.* **125** 63, 1939.

69 de Wesselow, O. L. V. S., and Thomson, W. A. R. A Study of Some Serum Electrolytes in Hypertension, *Quart. J. Med.* **8** 361, 1939.

70 Lindberg, H. A., Wald, M. H., and Barker, M. H. Renal Changes Following Administration of Hypertonic Solutions (50 Per Cent Sucrose, 50 Per Cent D-Sorbitol, 50 Per Cent Dextrose, and 10 Per Cent Sodium Chloride), *Arch. Int. Med.* **63** 907 (May) 1939.

The effect of alcohol on the kidneys of normal persons and on those of patients with Bright's disease has been studied by Bruger, Localio and Guthrie,⁷¹ who report that alcohol or whisky rarely augments the proteinuria of Bright's disease. Marked diuresis may follow its use even when the renal function is badly impaired. No deleterious effects were observed in normal subjects. In patients with nephrosclerosis there was sometimes observed to be a transient increase in the number of formed elements and a depression of function.

In some instances patients receiving sulfapyridine were found by Southworth and Cooke⁷² to suffer from hematuria, abdominal pain and nitrogen retention. This condition was attributed to the effects of the drug, since it cleared when the drug was withheld. Antopol and Robinson⁷³ observed the formation of uroliths in rats, rabbits and monkeys to whom sulfapyridine was given. The uroliths were formed by needle-like crystals of the acetyl derivative and were located most frequently at the level of the brim of the pelvis. They were not radiopaque, though calcium deposits were sometimes found about them. Toomey⁷⁴ has confirmed these reports of finding large concretions in the bladder, ureters and pelvis of the kidneys, which were hyperemic and enlarged and sometimes the seat of pyelonephritis. He warned against the use of sulfapyridine in the presence of nephritis and urinary retention, and in particular he warned against its use in poliomyelitis, since it has no effect in this infection.

Smadel and Swift⁴⁸ found sulfanilamide to be without deleterious effects on the course of experimental nephrotoxic nephritis.

A new method of producing renal ischemia and experimental hypertension has been devised by Page,⁷⁵ who induced proliferative perinephritis as a reaction to enclosing the kidneys in cellophane. Removal of the kidney so affected cured the hypertension. Denervation of the kidney does not prevent the occurrence of hypertension. He suggested that perinephritis may be an additional cause of hypertension in man.

71 Bruger, M., Localio, S. A., and Guthrie, N. W. Effect of Alcohol on Normal Kidney and the Kidney of Bright's Disease, *J. A. M. A.* **112** 1782 (May 6) 1939.

72 Southworth, H., and Cooke, C. Hematuria, Abdominal Pain, and Nitrogen Retention Associated with Sulfapyridine, *J. A. M. A.* **112** 1820 (May 6) 1939.

73 Antopol, W., and Robinson, H. Urolithiasis and Renal Pathology After Oral Administration of Sulfapyridine, *Proc. Soc. Exper. Biol. & Med.* **40** 428, 1939.

74 Toomey, J. A. Urinary Concretions and Sulfapyridine, *J. A. M. A.* **113** 250 (July 15) 1939.

75 Page, I. H. Production of Arterial Hypertension, *J. A. M. A.* **113** 2046 (Dec. 2) 1939.

Book Reviews

Clinical Gastroenterology By Horace Wendell Soper, M D, F A C P Cloth
Price, \$6 Pp 314, with 212 illustrations St Louis C V Mosby Company,
1939

This book is printed on an excellent quality of paper, the type is better than average, and the illustrations are generally good. Unfortunately, the material contained in the book does not measure up to the standards set by the publisher.

The author discusses diseases of the gastrointestinal tract. He includes, of course, diseases of the liver and biliary system and the pancreas. The content is principally the author's personal opinions and is mainly the result of his own large experience. Nothing particularly new is offered, although many portions of the book may be called novel. The advice that granulocytopenia be treated by intensive administration of nearsphenamine will cause many hematologists to shudder. Arsenic is under consideration as a cause of neutropenia, not as a cure.

The tirade against milk is an example of wishful, but hardly scientific, reasoning.

The discussion of the various dyspepsias (a poor term at best) leaves the reader confused and baffled. Another baffling chapter is the one on indicanuria. The reader is left with the conclusion that "indicanuria (and such symptoms as may be attributed to it) is amenable to general and hygienic treatment, but the reaction in the urine remains four-plus regardless of the improvement in the patient's condition."

The chapter on disease of the liver and of the gallbladder is totally inadequate. The pancreas is considered in two and one-half pages, one page of which deals with diabetes mellitus.

This list of examples, which could be extended, leaves the reader with the impression that the book was rather carelessly put together and that there was a lack of critical judgment in the preparation of the material. This impression is augmented by the appearance of poor English. "Diagnosis is of extreme importance as they are very amenable to operative treatment." This remark, set out as a separate sentence, is a little difficult to interpret. Colloquialisms are used with too great frequency. "The monkey wrench in the works" is understandable to the American reader but might not be so readily translated or understood by one whose education did not include the use of American slang.

Altogether the book has little to recommend it to the critical reader.

Chirurgie der Lungen und des Brustfelles By Alfred Brunner Price, 24 marks Pp 277 Dresden Theodor Steinkopff, 1938

This twenty-sixth volume of the "Medizinische Praxis" series is concerned primarily with the surgical diseases of the lung and pleura. Its purpose is the succinct compilation and presentation for the practicing physician of the material on surgical management of the commoner diseases of the lung and pleura. Accordingly, it succeeds in being a compendious review of these conditions. Obviously, completeness in respect to details must be sacrificed.

Among the conditions considered by the author are abscess and gangrene of the lung, bronchiectasis, pulmonary tuberculosis, empyema, tumors, parasitic diseases and fungous infection of the lung and pleura. The well established indications and rationale of the various methods of conservative and operative management of these conditions are discussed. Appropriately, the greatest amount of space is devoted to tuberculosis. The indications and various technics of collapse therapy are briefly described. In this regard better illustrations of the operative

technic of extrapleural thoracoplasty are considered desirable. There is an excellent author and subject index, and the incomplete but fairly representative indexed bibliography is helpful.

Les maladies de l'oesophage By J. Terracol, Professor of the Faculty of Medicine of the University of Montpellier. Price, 220 francs. Pp 664, with 352 illustrations. Paris: Masson et Cie, 1938.

This book by Terracol, written with the collaboration of 16 other persons interested in various fields of the subject, includes a detailed discussion of the diseases of the esophagus. The subject is presented in the usual fashion, including a discussion of anatomy, physiology and methods of study, such as the endoscopic technics and roentgenology, clinical syndromes of esophageal dysfunction and therapy. The subject is presented clearly and completely, with much space devoted to endoscopic procedures for study and therapy. The book is well illustrated, having 352 figures in all. At the end of each chapter there is appended a fairly large bibliography, which is almost entirely European, especially French.

This monograph represents much work and should prove to be of considerable value to those interested in gastroenterology and endoscopic procedures on the esophagus and to the internist, surgeon and roentgenologist, who frequently desire a book containing an accumulation and evaluation of the literature on the subject of diseases of the esophagus.

Surgical Anatomy By C. Latimer Callander, M.D., F.A.C.S. Second edition. Price, \$10. Pp 858, with illustrations. Philadelphia: W. B. Saunders Company, 1939.

The second edition of Callander's book on surgical anatomy is essentially the same as the first. In deleting discussions and illustrations which were out of date, the author has shortened the book by approximately 250 pages. Additions were made to include more recent advances in surgical anatomy, especially pertaining to surgery of the sympathetic nerves, syndromes involving the scalenus anticus muscle and cervical rib and the like. The book retains its lucid and practical features and should continue to be well received by surgeons.

News and Comment

American Board of Internal Medicine, Inc.—The American Board of Internal Medicine will conduct oral examinations previous to the meeting of the American College of Physicians in Cleveland and to the meeting of the American Medical Association in New York.

Applicants who have successfully passed the written examination and who plan to take the oral examination in 1940 should advise the office of the secretary at least six weeks in advance of the date of the examination they desire to take.

The next written examination will be given on October 21. Applications for this examination must be filed in the secretary's office by September 1.

Application forms may be obtained from Dr. William S. Middleton, secretary-treasurer, 1301 University Avenue, Madison, Wis.

SUDDEN OCCLUSION OF CORONARY ARTERIES FOLLOWING REMOVAL OF CARDIO- SENSORY PATHWAYS

AN EXPERIMENTAL STUDY

C G McEACHERN, M D, B Sc (MED)

G W MANNING, M A

AND

G E HALL, M D, PH D

TORONTO, CANADA

In a previous paper ¹ experiments were reported showing that in dogs morphine and ether anesthesia markedly reduced the mortality rate after ligation of coronary arteries. In those experiments sudden death following ligation of the circumflex branch of the left coronary artery in the anesthetized dogs occurred in 25 per cent. Similar ligation in dogs in the conscious state resulted in a mortality rate of 75 per cent. Again, when ligation of the anterior descending branch of the left coronary artery was effected with anesthesia the mortality rate was less than 10 per cent, while similar ligation in conscious animals was followed by an increase in the mortality rate to approximately 40 per cent.

From direct and indirect observations on the conscious animals in that series of experiments it was suggested that in addition to the primary ischemic area produced by such ligation other areas of myocardium were rendered ischemic by a possible reflex spasm of the collateral coronary arteries and arterioles. The reflex mechanism was believed to be initiated by metabolites produced in the ischemic area initiating afferent impulses which, in turn, produced efferent vagal impulses, causing constriction of the medium-sized and smaller-sized coronary arteries. The marked reduction in mortality when ligation was performed with a surgical degree of anesthesia suggested that this reflex mechanism had been depressed.

Aided by a grant from the Josiah Macy Jr Foundation, New York

From the Department of Medical Research, Banting Institute, University of Toronto Faculty of Medicine

¹ Manning, G W, McEachern, C G, and Hall, G E. Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches, *Arch Int Med* 64 661-674 (Oct) 1939

We believe that this reflex mechanism alone is not completely responsible for the higher mortality in the conscious animal. As a result of our previous experiments it would appear, also, that certain areas of the myocardium are more readily influenced by ischemic processes than other regions and that ectopic beats, tachycardia and ventricular fibrillation are more readily initiated when these highly irritable regions become ischemic.

We believe also that the degree of pain experienced by the animals after ligation of the coronary artery in the conscious state might play a part in increasing the mortality rate under these conditions. In this connection it is only necessary to mention here that the cardiosensory pathways are located in the cervical and thoracic cardiac nerves and pass through the stellate and upper five thoracic ganglions on their way to the spinal cord. After the complete removal of these ganglions animals should not experience any pain as a result of ligation of the coronary artery.

The purpose of the present paper is to report the results of experiments which show that the removal of the cardiosensory pathways protects the animal from pain and sudden death after ligation of the coronary artery in the conscious state.

Three groups of experiments were carried out in this series. In the first group partial cardiosensory denervation was produced by removal of the stellate and upper five thoracic ganglions on one side only. Pain was decreased, and the mortality following ligation of the large left circumflex branch was reduced. In the second group, in which complete cardiosensory denervation was produced, ligation of the smaller anterior descending branch resulted in no sudden deaths, and no pain was evidenced. In the third group complete cardiosensory ligation of the large left circumflex branch resulted in a marked decrease in the mortality rate, and again no pain was evidenced.

The possible clinical significance of this work will be discussed later in the paper.

EXPERIMENTS

Forty-six normal adult dogs used in this series were divided into three groups. In group 1 the left stellate and upper five thoracic ganglions were removed. At the same operation a loose ligature was placed around the circumflex branch of the left coronary artery close to its origin. The two ends of the loose ligature were brought to either end of the incision, the thorax was closed, and a sterile dressing was placed over the wound. The animal was allowed to recover from the anesthesia (morphine and ether). The following day ligation of the artery was effected by sudden traction on the ends of the ligature.

In group 2 the stellate and upper five thoracic ganglions were removed bilaterally. At a subsequent operation a loose ligature was

placed around the anterior descending branch of the left coronary artery, and the animals were then treated as in group 1

The animals in group 3 were prepared in a similar manner to those in group 2 except that the circumflex branch of the left coronary artery was ligated

Several normal electrocardiograms were taken on all dogs while they were lying on their right sides prior to any surgical intervention. Records were taken before, during and at varying intervals after ligation. In some instances continuous blood pressure recordings were made. Immediately autopsy was performed on all animals which died.

Although the surviving animals were kept quiet for a few hours, no attempt was made to limit their activities after this time. Some deaths from cardiac failure, resulting from overexertion in the presence of a damaged myocardium, would be expected. In spite of this eventuality deaths occurring within twenty-four hours of ligation were listed as "sudden deaths."

GROUP 1—Sudden occlusion of the left circumflex branch in animals following removal of the stellate and upper five thoracic ganglions on the left side

Twelve dogs were used in this group. Only slight cardiac pain was evidenced after sudden ligation of the artery in the conscious state. Dyspnea, restlessness, shock and sudden loss of consciousness were not observed in the animals which survived the sudden occlusion.

In this group 8 survived and 4 died within twenty-four hours. This gives a probable mortality rate of 33 per cent. One dog died in twenty-one hours and showed marked atelectasis on one side and pulmonary edema on the other. Two died in about four hours and showed definite signs of pulmonary congestion, some edema and engorgement of the right side of the heart. The fourth animal stopped breathing in nine minutes, and continuous electrocardiograms indicated a heart block (fig 1).

Electrocardiographic Changes—Within a few seconds of ligation there was an elevation of the RT segment, which became progressively more marked and reached its maximum within five minutes (fig 2B). At this time a slight elevation of the RT segment was observed in lead I, while the elevation of this segment in leads II and III was so great that the T wave was hardly discernible.

The RT segment then began to recede toward the isoelectric level (fig 2C). After a period of hours the Q wave increased in amplitude, and the RT segment in leads II and III remained elevated. The PR interval was normal (fig 2D). The record taken one day after ligation showed a low voltage of the R wave and a widening of the QR interval in lead I (fig 2E). The PR interval was irregular. After two days the RT segment was depressed and had assumed a rounded appearance.

Many of the typical abnormalities as seen in the later records persisted for from three weeks to three months.

GROUP 2—Sudden occlusion of the anterior descending branch in conscious dogs following bilateral removal of the stellate and upper five thoracic ganglions

Twelve animals were used in this group of experiments. The left anterior descending branch was ligated suddenly in the manner already described. Cardiac pain, dyspnea, restlessness or shock was not observed after the ligation. The

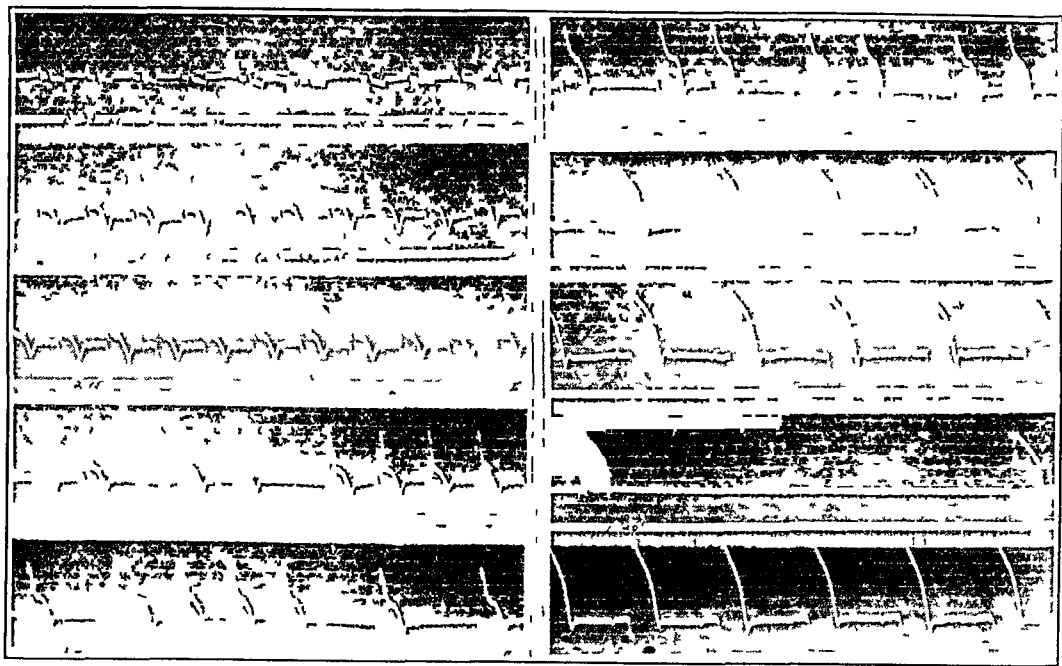


Fig 1 (group 1)—Electrocardiogram (lead II) showing fatal heart block following ligation of the left circumflex branch after removal of the left stellate and upper five thoracic ganglions



Fig 2 (group 1)—Typical electrocardiogram (leads I, II and III) taken after ligation of the left circumflex branch after removal of the left stellate and upper five thoracic ganglions

animals were exceedingly quiet, in contrast to animals in which similar ligations were carried out when the stellate and thoracic ganglions were intact

Changes in blood pressure were not great. An initial decrease of about 20 mm of mercury occurred some twenty seconds after ligation. However, within a few minutes the blood pressure had returned almost to normal.

No deaths occurred within twenty-four hours in this group. One animal died of infection on the third day, the remaining animals survived indefinitely. There were no deaths referable to the condition of the heart.

Electrocardiographic Changes—The most characteristic features of the electrocardiographic records taken from the animals in this group were an elevation of the RT segment in lead I and a depression of the ST segment in leads II and III (fig 3). This depression was apparent within a few seconds after ligation and



Fig 3 (group 2)—Typical electrocardiogram (leads I, II and III) taken after ligation of the left anterior descending branch after removal of the stellate and upper five thoracic ganglions bilaterally.

reached its maximum in about five minutes. The depressed ST segment at this time showed an upward convexity. The depression became progressively less marked after ten minutes, and in about four hours the ST segment had returned almost to the isoelectric level, the T wave remaining markedly negative. The contour of the T wave changed during the next forty-eight hours, and at the end of this time the T wave was upright and of high amplitude. The records in all three leads were essentially normal within fourteen days.

GROUP 3—Sudden occlusion of the left circumflex branch in conscious animals following bilateral removal of the stellate and upper five thoracic ganglions

Twenty-two animals were used in this group of experiments. The artery was ligated in the conscious animals in the manner previously described. In only 2 animals was there any evidence of cardiac pain, both of these appeared to be

recovering, when suddenly ventricular tachycardia set in. Fatal ventricular fibrillation rapidly supervened, and the dogs died in nine and fifteen minutes, respectively, after ligation. Severe dyspnea in the absence of cardiac pain was observed in another case. This animal had prolonged and severe heart block which did not prove fatal (fig 4).

No other animals died suddenly within twenty-four hours. The probable mortality rate was 9 per cent. The low mortality rate is of more significance in this group than in group 2, since the left circumflex branch supplies a much larger area of myocardium than does the anterior descending branch. Three delayed deaths occurred (within twenty-four to forty-eight hours) from cardiac failure, as indicated by pulmonary edema and congestion of the right side of the heart.

Electrocardiographic Changes—With the exception of the 3 animals previously mentioned (the 2 dying with ventricular fibrillation and the 1 surviving a severe

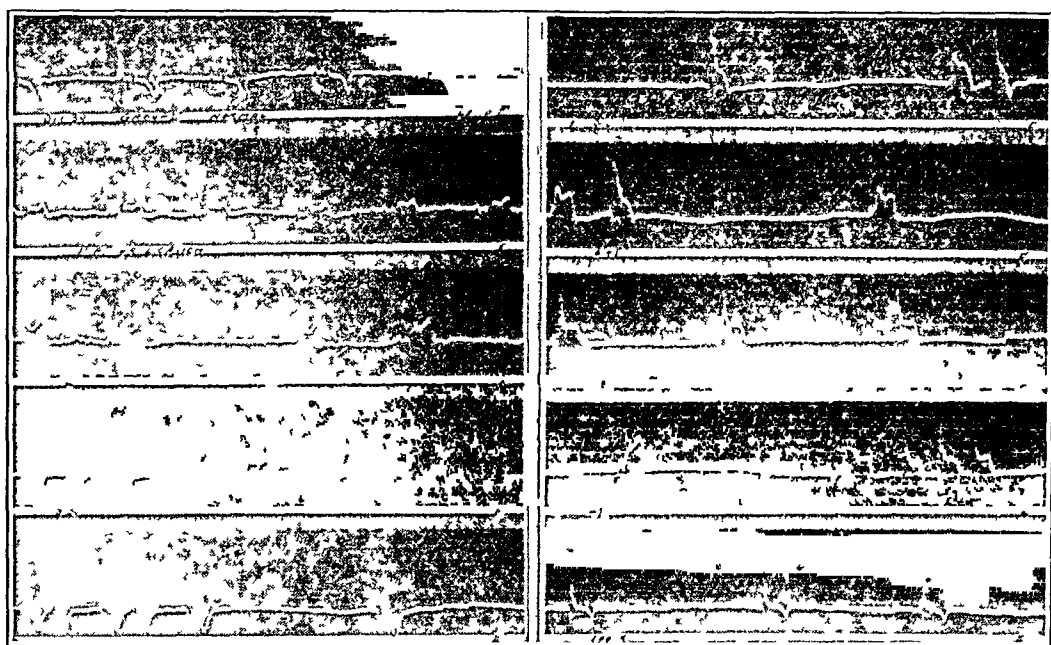


Fig 4—Electrocardiogram (lead II) showing severe heart block following ligation of the left circumflex branch after removal of the stellate and upper five thoracic ganglions bilaterally.

heart block) the electrocardiographic changes obtained in the animals in this group were uniform. The records of a typical experiment will be described.

A marked elevation of the RT segment occurred within thirty seconds (fig 5) and was accompanied by a progressive increase in the amplitude of the ventricular complex, which reached its maximum in about five minutes (fig 5B). The record taken at this time showed a high take-off of the RT segment, ending negatively in lead I. The high take-off of the elevated RT segment from the downstroke of the R wave was noticeable in leads II and III. The PR interval remained prolonged.

A few extrasystoles of left ventricular origin were noted periodically in leads II and III (fig 5C). The PR interval was decreased.

No further significant changes in the electrocardiograms were noted until about six hours after ligation (fig 5D). A few ventricular extrasystoles persisted, and a complete dissociation between auricular and ventricular complexes was found.

Further changes in the electrocardiographic record took place in twenty-four hours (fig 5 *E*), after which time the form of the record became more stable, and at forty-eight hours the record was typical of axis deviation (fig 5 *F*)

The time required for the electrocardiograms to return to normal varied in different animals. Changes could frequently be observed over a period of weeks.

COMMENT

In the experiments reported in this paper we have attempted to investigate further the reflex mechanisms which we believe to be responsible for the high percentage of sudden deaths following experimental ligation of large branches of the coronary artery in conscious animals.

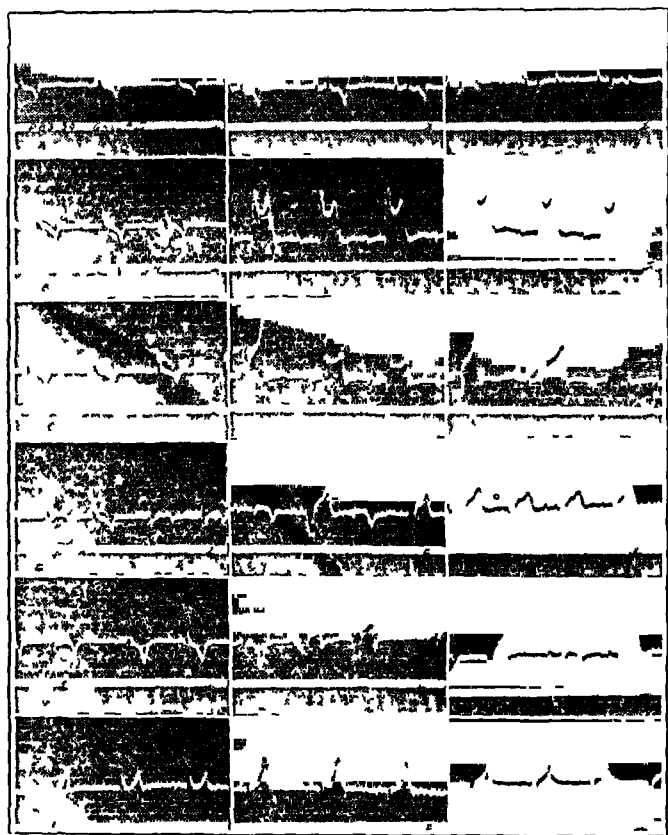


Fig 5 (group 3)—Typical electrocardiogram (leads I, II and III) taken after ligation of the left circumflex branch after the removal of the stellate and upper five thoracic ganglions bilaterally.

In brief, we have previously shown that (1) ligation of the left anterior descending branch in the anesthetized animal resulted in a mortality rate of less than 10 per cent, while ligation of the same branch in the conscious animal was attended by a mortality rate of about 40 per cent, (2) ligation of the larger left circumflex branch in the anesthetized animal resulted in a mortality rate of about 25 per cent, and when this ligation was performed in the conscious animal the mortality rate increased to 75 per cent, and (3) the animals which died

suddenly after the ligation of either the anterior descending or the circumflex branch in the conscious state all showed ventricular extrasystoles, tachycardia and terminal ventricular fibrillation (figs 6 and 7)

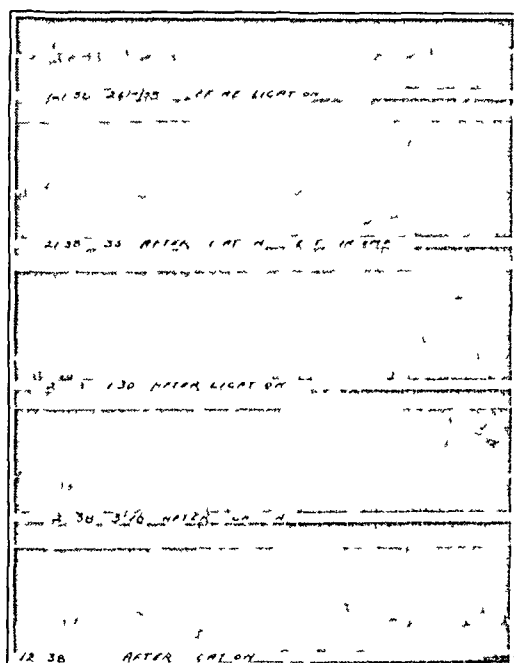


Fig 6—Electrocardiogram (lead II) showing fatal ventricular fibrillation following ligation of the left circumflex branch in a conscious animal

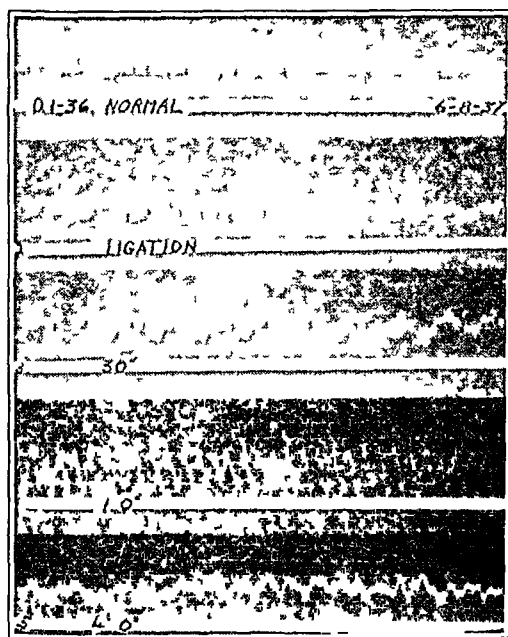


Fig 7—Electrocardiogram (lead II) showing fatal ventricular fibrillation following ligation of the left anterior descending branch in a conscious animal

It is possible, however, that in a larger series of experiments some animals might have died suddenly from heart block

It appeared from these experiments that the increased mortality following ligation in conscious animals was due to some reflex mechanism causing either spasm of collateral coronary arterioles or an altered irritability of the myocardium which permitted ventricular fibrillation to be more readily initiated.

This theoretic but possible reflex mechanism was apparently interrupted by the bilateral removal of the stellate and upper five thoracic ganglions, since the mortality following ligation of the larger left circumflex branch in the conscious animal was reduced from 75 per cent to 10 per cent as a result of such surgical intervention. Ventricular extrasystoles were present in only a few instances, ventricular tachycardia was infrequently noted, and ventricular fibrillation was observed in only the 2 dogs which died.

When the stellate and upper five thoracic ganglions had been removed on only the left side (group 1) acute ligation of the left circumflex branch in the conscious state resulted in a mortality rate of about 33 per cent. One of the animals dying while under observation showed electrocardiographic evidence of complete heart block (fig 1). Ventricular fibrillation was not observed in any of the animals in this group. From this fact it was believed that even the removal of the cardiac sympathetic nerves on one side prevented to a great extent the mechanisms which may have been responsible for the high mortality rate following coronary artery ligation in intact conscious animals.

When the left anterior descending branch (group 2) was ligated after the bilateral sympathetic denervation of the heart the mortality rate was 0. Again, extrasystoles were relatively infrequent. Ventricular tachycardia and ventricular fibrillation were not observed.

It would appear that ablation of the cardiosensory pathways not only prevented pain after temporary coronary occlusion, as has been shown by White, Garrey and Atkins,² but also decreased materially the incidence of ventricular fibrillation and the mortality in animals after permanent occlusion. Again, it should be emphasized that the size of the infarcts produced in these animals was essentially the same as in the groups with intact cardiac sympathetic nerves after ligation of a similar coronary artery branch. The decrease in mortality possibly results from the interruption of the reflex arc, preventing afferent impulses from reaching the vasoconstrictor center and thus eliminating reflex spasm of collateral coronary arteries. On the other hand, it may be that sympathetic denervation has rendered the myocardium less susceptible to the onset of ventricular fibrillation. Possibly both mechanisms have been affected.

² White, J. C., Garrey, W. E., and Atkins, J. A. Cardiac Innervation: Experimental and Clinical Studies, *Arch Surg* 26:765 (May) 1933.

On the basis of the anatomic distribution of the sympathetic nerves to the heart it appears that removal of the stellate ganglions would not be as effective in decreasing the mortality following ligation of the coronary artery as would a more complete sympathetic denervation of the heart

It is important to mention in this connection that the sensory pathways lie in the thoracic cardiac nerves as well as in the inferior and middle cervical cardiac nerves. In order to abolish pain completely it is necessary to remove the whole sensory supply of the heart. It is possible that when the sensory pathways are completely interrupted the mechanism responsible for the onset of fatal ventricular fibrillation may likewise be eliminated to a great extent.

Although one should not, and in many cases cannot, apply to human beings the direct results of animal experimentation, it is, in this instance, tempting to try to correlate our experimental observations with clinical observations on patients with angina pectoris. In this connection there is the possibility that patients suffering from this condition as well as from coronary thrombosis have a particularly susceptible nervous system. Their reflex nervous mechanisms may perhaps be much more sensitive than those in the ordinary person. Mild or moderate exertion, cold air and emotion are some of the activities which may precipitate an attack of angina pectoris in a susceptible person, but it could hardly be said that the average person would likewise be affected.

Patients with angina pectoris have a life expectancy of approximately five years. In these patients the incidence of sudden death is high. In view of these two facts it does not seem unreasonable to assume that bilateral sympathetic denervation of the heart may still have a sound clinical application. Such surgical intervention might protect these patients from pain and at the same time from sudden death which so frequently occurs.

SUMMARY

Removal of the cardiosensory pathways eliminates the pain and markedly reduces the mortality rate after sudden and permanent occlusion of the larger branches of the left coronary artery in the conscious dog.

PROGRESS IN CHEMOTHERAPY OF BACTERIAL AND OTHER DISEASES

WITH SPECIAL REFERENCE TO THE PRONTOSILS, SULFANILAMIDE
AND SULFAPYRIDINE

JOHN A. KOLMER, M.D.

Professor of Medicine, Temple University School of Medicine, and Director
of the Research Institute of Cutaneous Medicine

PHILADELPHIA

Until the discovery of the effectiveness of the original prontosil (the hydrochloride of 4-sulfonamido-2',4'-diaminoazobenzene) in the treatment of streptococcal and staphylococcal infections the chemotherapy of systemic bacterial diseases was largely disappointing. It is true that certain dyes, like gentian violet and acriflavine base as well as various mercurial compounds, commanded considerable attention and extensive clinical trial, with encouraging results in individual cases, but in general, original hopes and expectations were not realized. Indeed, aside from the helpful effects of neoarsphenamine in the treatment of anthrax and the clinically inapplicable treatment of pneumococcal infections with ethylhydrocupreine (optochin) base and its soluble derivative ethylhydrocupreine hydrochloride, the only site in which bacteria have been found vulnerable by systemic chemical attack has been the urinary tract, where conditions are exceptional. But, as I wrote in 1936

I by no means share the skepticism so frequently expressed in regard to the future of the chemotherapy of bacterial diseases if money and interested workers are available for the tremendous expense and labor required for advancing our knowledge. It is true that more, much more, advance has been made in the chemotherapy of protozoal and metazoal diseases and that the problems of bacterial diseases are apparently more difficult, but when one considers the advances made during the past five years it is neither rash nor unwise to expect greater discoveries in the future as the fruit of hard, conscientious and unremitting, but systematized toil coupled with the ever alluring chance of making a "lucky strike."

It is only a few years since this "lucky strike" was made, in the discovery of the remarkable chemotherapeutic properties of the prontosils and sulfanilamide, followed by sulfapyridine, and their known effective scope is widening so rapidly and with brilliant success in so many directions, yet with much ground remaining to be explored, that the ultimate consequences of their discovery cannot be predicted. Definite knowledge, however, has been masked by publications which are speculative, statistically vulnerable or so irrelevant as to be of little value, hence it appears that a review of the more recent literature bearing on the use of these

compounds in experimental infections and human disease may be helpful, particularly since only a few persons are in position to assimilate it except in predigested or concentrated form

HISTORICAL SURVEY OF COMPOUNDS REVIEWED

Thirty-two years ago Gelmo synthesized paraaminobenzenesulfonamide, now universally known as sulfanilamide, but its medicinal value was neither suspected nor studied. In 1909 Horlein, Dressel and Kothe (*Deutsches Reichpatent* 226230, 226235, 226239, 226240, 226594 and 226777) prepared azo dyes with sulfonamide and substituted sulfonamide groups, one of which possessed a limited therapeutic effect in experimental hemolytic streptococcic infections of mice but received little attention. Further investigation under Domagk resulted in the production of the hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene, a brick red powder relatively insoluble in water (0.25 per cent), which was included in the German patent granted Mietzsch and Klarer in 1932 (*Deutsches Reichpatent* 607537) covering several sulfonamide-containing azo dyes and to which the trade name "prontosil" was given. This has subsequently been designated as "the original prontosil" and, while no longer employed, has the distinction of being the compound used by Foerster in 1933, under the name "streptozon," in the first recorded instance of treatment of a human being (a child) with staphylococcic septicemia resulting in recovery. Doubtless the name used by Foerster was due to his knowledge of the fact that Domagk had employed the compound in 1932 in the treatment of experimental streptococcic infections of mice, although it was not until 1935 that Domagk published his epoch-making paper announcing the remarkable therapeutic effectiveness of the original prontosil not only on experimental streptococcic infections of mice and rabbits but to some extent on staphylococcic infections of rabbits as well, and thereby introducing to the world an agent constituting one of the greatest discoveries in the history of chemotherapy.

In the same issue of the *Deutsche medizinische Wochenschrift* appeared three clinical reports attesting the efficacy of the original prontosil in various streptococcic infections as well as in infections of the urinary tract due to the colon bacillus. Later in the same year Domagk announced a new soluble derivative, the disodium salt of 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate, called prontosil S or prontosil soluble, which he stated was just as effective as the original prontosil in streptococcic and staphylococcic infections and also possessed a certain degree of therapeutic effect on pneumococcic infections of types I and II in mice, this compound is now marketed in the United States under the name of neoprontosil in tablets and in a 5 per cent solution.

In 1936 the Tréfouels, Nitti and Bovet found that the effective azo dyes broke down in the tissues at the azo linkage to paraaminobenzenesulfonamide, the compound first synthesized by Gelmo in 1908, and suggested that the therapeutic effectiveness of the original and of the soluble prontosil was due to this white powder, which was called prontosil album and later since of worldwide renown, sulfanilamide, the name given it by the Council on Pharmacy and Chemistry of the American Medical Association on April 17, 1937. This discovery, coupled with the fact that it was not protected by patents, led rapidly to its widespread manufacture and use, as well as to the preparation and testing of a large number of various new derivatives, although clinical experience lends some support to Domagk's contention that the effectiveness of the prontosils is not entirely due to their reduction to sulfanilamide in the body, especially in certain streptococcic infections.

Expert chemists have carefully studied the chemical structure of many new derivatives but have been unable to learn what makes one compound more therapeutically active and less toxic than another closely related one. Thus, proseptasine or septazine (parabenzylaminobenzenesulfonamide, N^4 -benzylsulfanilamide) is a compound in which substitution has been made in the amino group without superior properties, but this is a familiar story in chemotherapy, where Nature is loath to give up her secrets on chemical constitution in relation to disinfection. Indeed, only actual trials in the living animal for both toxicity and therapeutic effectiveness serve as criteria, and no one knows how many compounds are at present on the shelves of laboratories which may have valuable chemotherapeutic properties.

However, two compounds in which one hydrogen atom of the sulfonamide group has been substituted have been found highly effective, namely, sulfanilyldimethylsulfanilamide (known commercially chiefly as uleron or ulron) for gonococcic infections and sulfapyridine for pneumococcic infections. The former, which is paraaminobenzenesulfonylparaaminobenzenedimethylsulfonamide, is relatively insoluble in water and is administered orally, but a soluble sodium salt for parenteral administration is now available. The latter, which is 2-(paraaminobenzenesulfonamido)-pyridine and which is also sold commercially as M & B 693 and as dagenan, is likewise relatively insoluble in water, but a soluble sodium salt for parenteral administration has been prepared. In this connection it is interesting to note that Kolmer, Brown and Raiziss were first to use pyridine compounds in the chemotherapy of experimental streptococcic infections, of which one (2-2'-pyridyl sulfide dihydrobromide) was as effective as neoprontosil although not of the same structure as sulfapyridine, which is a combination of sulfanilamide with alphaaminopyridine.

For the purposes of this review, therefore, which is largely confined to those compounds which have been subjected to trial in the treatment of both experimental infections and various diseases, only the prontosils,¹ sulfanilamide, sulfanilyldimethylsulfanilamide and sulfapyridine are chiefly considered, because a review of results observed with the large number of allied compounds in experimental infections alone would add greatly to its length and lead me too far afield from clinical applications. Furthermore, no attempt has been made to review the entire vast literature on these particular compounds, I have tried only to include a sufficient number of the more important articles to justify an expression of opinion of their value in the treatment of various experimental and human infections. Detailed and excellent reviews in book form have been published by Mellon, Gross and Cooper and more recently by Long and Bliss.

THE THERAPEUTIC EFFECTS

Streptococcic Infections—It is well proved that the prontosils, sulfanilamide and sulfapyridine are highly effective in the treatment of mice in which intraperitoneal inoculation with hemolytic streptococci belonging to group A of Lancefield has resulted in peritonitis with an associated septicemia (table 1). The most striking results have been observed with streptococci of high virulence for mice, because a minimal lethal dose of such organisms contains only a small number of cocci, and the prontosils, as well as sulfanilamide and sulfapyridine, act better on a sparse and scattered bacterial population than on highly concentrated masses of bacteria.

Furthermore, these compounds do not appear to be as readily acetylated in mice as in rabbits, with the result that more free sulfanilamide is available in the blood and tissues for bacteriostatic effects. This probably accounts for the fact that the prontosils and sulfanilamide have proved less effective in the treatment of intradermal beta hemolytic streptococcic infections of rabbits with associated septicemia and suppurative arthritis, as employed by Kolmer and Rule in 1937 for chemotherapeutic investigations, because they provided experimental lesions more closely resembling streptococcic infections of human beings.

Owing to the low virulence of nonhemolytic streptococci for mice and rabbits, neither compound has been generally employed in therapeutic tests. Muether and Kinsella found sulfanilamide effective in the

1 In the text and in the tables "original prontosil" refers to the hydrochloride of 4-sulfamido-2'-4'-diaminoazobenzene. "Soluble prontosil" and "neoprontosil" refer to disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate, which is now marketed under the proprietary name "neoprontosil". Since this review was prepared, the Council on Pharmacy and Chemistry of the American Medical Association has adopted "azosulfamide" as the nonproprietary name for the latter compound.

treatment of experimental bacterial endocarditis of dogs due to *Streptococcus viridans*, but, as will be shortly discussed, the prontosils, sulfanilamide and sulfapyridine have generally failed in the treatment of *Streptococcus viridans* endocarditis of human beings so far as complete recovery is concerned, the same is true of *Streptococcus faecalis* infections of the urinary tract

Most experimental investigations have been conducted with group A streptococci. Whether or not sulfanilamide varies in effectiveness with the remaining groups cannot be stated except to mention that the results of *in vitro* studies have shown groups A and C most susceptible,

TABLE 1—*Experimental Hemolytic Streptococcic Infections*

Authors	Compounds	Animals	Treated		Controls	
			Number	Percentage of Survivors	Number	Percentage of Survivors
Domagk	Original prontosil	Mice	12	100		
Levaditi and Vaisman	Original prontosil	Mice	8	37.5	3	0
Gley and Girard	Original prontosil	Mice	50	38	50	0
Buttle, Gray and Stephenson	Sulfanilamide and derivatives	Mice	138	43	96	0
Cooper, Gross and Lewis	Sulfanilamide	Mice	44	65	44	27
Long and Bliss	Soluble prontosil	Mice	84	37	64	0
Long and Bliss	Sulfanilamide	Mice	18	67		
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	55	64 to 66	100	0
Raiziss, Severac, Moetsch and Clemence	Soluble prontosil	Mice	55	28 to 63		
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	60	74		
Raiziss, Severac, Moetsch and Clemence	Sulfanilamide	Mice	150	37 to 60		
L. E. H. Whitby	Sulfapyridine	Mice	156	31.7 days	126	0.417 days
Kolmer, Raiziss, Rule and Brown	Soluble prontosil	Mice	12	50	8	0
Kolmer, Raiziss, Rule and Brown	Soluble prontosil	Rabbits*	3	Effective		
Kolmer, Raiziss, Rule and Brown	Sulfanilamide	Rabbits*	45	Effective		

* Intradermal lesions and arthritis

groups B, E and G variable and group D quite insusceptible. Lockwood, Coburn and Stokinger, however, reported that no type seemed refractory to the compound in human infections and that groups C and G as well as group A seemed to be influenced by sulfanilamide therapy.

Hemolytic Streptococci In this connection the studies of Spaulding and Bondi in my laboratory are also significant in indicating that infections with anaerobic hemolytic streptococci of mice are much less susceptible to the therapeutic activity of sulfanilamide and sulfapyridine than infections with aerobic strains. Since temporarily or permanently anaerobic hemolytic streptococci may be found in a large percentage of hemolytic streptococcic infections in human beings, this may offer an explanation of the failure of sulfanilamide and sulfapyridine in the

treatment of some cases of puerperal sepsis and other hemolytic streptococcic infections, as stated by Colebrook and Kenny. Thus an obligate anaerobic hemolytic streptococcus of group A was found highly insusceptible to sulfanilamide and sulfapyridine in the treatment of infections of mice, while a second strain was found moderately susceptible. A strain which was temporarily anaerobic, however, was moderately responsive to both compounds.

From the experimental standpoint it is difficult to draw any conclusions on the comparative therapeutic effects of the prontosils, sulfanilamide and sulfapyridine in the treatment of hemolytic streptococcic infections of mice. In terms of the actual amounts given in grams per kilogram of body weight, however, both the prontosils and sulfapyridine appear to be somewhat more effective than sulfanilamide. Of additional interest and importance is the question of simultaneous administration of antistreptococcus serum. Loewenthal has recently stated that the combination treatment with serum and sulfanilamide for streptococcic infections of mice gave better results than either alone and that these two therapeutic agents act in a different but complementary manner.

Since the prontosils and sulfanilamide were first identified with the treatment of streptococcic infections in human beings, it is to be expected that the largest part of the literature has been devoted to them. One unfortunate result has been the indiscriminate use of these compounds in the treatment of all sorts of infections on the basis of clinical rather than bacteriologic diagnosis. As expected under the circumstances, infections due to nonhemolytic types of streptococci have been included, although fortunately most serious streptococcic infections of human beings are due to hemolytic streptococci of group A. As a result there is a greater uniformity of opinion regarding the effectiveness of the prontosils, sulfanilamide and sulfapyridine in the treatment of severe infections, especially septicemia, including puerperal sepsis, surgical cellulitis and lymphadenitis and erysipelas, than of minor infections.

(a) *Puerperal Sepsis* Among the first to attract favorable attention was the treatment of puerperal fever with the original and soluble prontosils and sulfanilamide by Colebrook and Kenny, who reported a mortality of about 4.7 per cent in 64 patients and later about 7 per cent in 115 patients treated with sulfanilamide (table 2), as contrasted with a mortality of about 22.8 per cent when former methods of treatment were used. These results have been generally confirmed and have proved the great value of the compounds in the treatment of puerperal endometritis due to hemolytic streptococci, as well as in postabortal septicemia, especially since most of the deaths were mainly due to causes beyond the influence of treatment, such as pulmonary and cerebral embolism and hemorrhage. In addition to reduction in mortality there has been

a distinct reduction in the average time of illness and the frequency of general peritonitis, and apparently Colebrook is of the opinion that the soluble prontosil (neoprontosil) may be more effective than sulfanilamide

TABLE 2—*Systemic Streptococcic Infections*

Authors	Diseases	Compounds	Number of Patients	Results
Colebrook and Kenny	Puerperal sepsis	The prontosils and sulfanilamide	115	93 per cent recoveries
Fouls and Barr	Puerperal sepsis	Soluble prontosil and sulfanilamide	22	98.6 per cent recoveries
Snodgrass and Anderson	Erysipelas	The prontosils and sulfanilamide	135	Effective
Nelson, Rinzler and Kelsey	Erysipelas	Sulfanilamide	344	97.38 per cent recoveries
Sako, Dwan and Platou	Scarlet fever	Sulfanilamide	100	Reduction in complications
Peters and Howard	Scarlet fever	Sulfanilamide	150	Reduction in complications
Colebrook and Kenny	Puerperal peritonitis	The prontosils	10	90 per cent recoveries
Hageman and Blake	Pneumonia	Sulfanilamide	7	100 per cent recoveries
Major and Leger	Subacute endocarditis*	Soluble prontosil	1	Alleged effective
Klee and Romer	Subacute endocarditis	Original prontosil	5	Ineffective
Ellis	Subacute endocarditis	Sulfapyridine	2	Temporarily improved
L. Whitby	Subacute endocarditis	Sulfapyridine	3	Temporarily improved
Barnett, Hartman, Perley and Ruhoff	Subacute endocarditis	Sulfapyridine	1	Temporarily improved
Saller	Subacute endocarditis	Sulfanilamide	1	Ineffective
Kelson and White	Subacute endocarditis	Sulfapyridine and heparin	1	3 apparently cured
Bliss, Long and Feinstein	Subacute endocarditis	Sulfanilamide	3	No recoveries
Spink and Crago	Subacute endocarditis	Sulfanilamide	11	1 apparently cured
Bannick, Brown and Foster	Ulcerative colitis	Neoprontosil and sulfanilamide	9	Effective
Collins	Ulcerative colitis	Sulfanilamide	11	Favorable in 73 per cent
Brown, Herrell and Bargin	Ulcerative colitis	Neoprontosil	8	Favorable

* Due to *Streptococcus viridans*

(b) Septicemia Excellent results have also been reported in the treatment of hemolytic streptococcic septicemia of surgical origin complicating wounds and burns, with associated lymphadenitis. My personal experience in 18 cases during the past three years has been favorable. In each case there were one or more positive blood cultures. Recovery occurred in 14 cases, with a mortality of about 22 per cent. Treatment consisted of surgical drainage and oral administration of neoprontosil.

and sulfanilamide, along with blood transfusions and intravenous administration of antistreptococcus serum

(c) Erysipelas There is almost complete unanimity of opinion on the uniformly good results observed in the treatment of simple uncomplicated erysipelas of both adults and children. In general terms the mortality in adults treated with antitoxin has been about 10 per cent and in infants and children, from 30 to 50 per cent, whereas after treatment with the prontosils and sulfanilamide these rates have been reduced to about 2 and 5 to 12 per cent, respectively. This may be due in large part to the vascularity of the lesions, which allows good access of free sulfanilamide in the blood. Such results are certainly much more favorable than those in cases in which there is some other complicating condition, like abscess or septic thrombi, in which the mortality has continued high in spite of neoprontosil and sulfanilamide therapy.

(d) Scarlet Fever In cases of scarlet fever the compounds have not materially shortened the duration of fever or shown any marked effects on the rash, nor are such effects to be expected, since sulfanilamide apparently possesses but feeble neutralizing or inactivating power on exogenous toxins, including most likely the erythrogenic toxin of this disease. The compounds have apparently proved of value, however, in materially reducing the percentage of complications, like otitis media, mastoiditis, lymphadenitis and nephritis, by inhibiting the aggressiveness of the streptococci. For this reason it appears that the treatment of scarlet fever, in so far as specific therapy is concerned, may consist in the administration of convalescent serum or antitoxin for combating the early toxemia of the disease and of neoprontosil or sulfanilamide for combating the invasiveness of the streptococci themselves.

(e) Meningitis One of the most impressive results observed with neoprontosil and sulfanilamide has been in the treatment of streptococcic meningitis (table 3), with which the mortality has been hitherto almost 100 per cent. Kolmer, Rule and Werner treated 46 rabbits with experimental hemolytic streptococcic meningitis with sulfanilamide and recorded the recovery of 20 per cent, whereas all of 12 untreated controls succumbed, of 12 monkeys 58 per cent recovered, with fatal results in 2 untreated controls. Of course, nothing else of value in the treatment of this highly mortal disease can be overlooked, especially adequate drainage of the primary foci of infection, so likely to be mastoiditis or sinusitis, along with drainage of the cerebrospinal fluid every eight to twelve hours. Oral or parenteral administration is preferred, it is doubtful if intrathecal injections of the compounds are indicated, although both neoprontosil and sulfanilamide are well borne by this route of administration. Apparently sulfanilamide is the compound of choice. While streptococcic meningitis is usually due to hemolytic types, a few patients

recovering under sulfanilamide therapy are believed to have had conditions due to nonhemolytic types, including *Str viridans*, however, the condition may have been really caused by a hemolytic streptococcus stabilized in the viridans phase. My personal experience is confined to 5 cases, in which the condition was secondary to mastoiditis or nasal accessory sinusitis and in which sulfanilamide was administered, with 3 recoveries.

(f) Tonsillitis, Pharyngitis, Laryngitis and Cervical Adenitis. Many authors have reported favorable results in the treatment of acute tonsillitis, pharyngitis and laryngitis, but extensive studies are few. In many cases, however, no improvement has been shown, and certainly neoprontosil and sulfanilamide by oral administration and local application

TABLE 3—*Streptococcic Meningitis*

Authors	Compounds	Number of Patients	Percentage of Recoveries
Schwentker and others	Sulfanilamide	4	75
Neal and Applebaum	Soluble prontosil	17	76
Neal	Sulfanilamide	26	81
Trachler, Frauenberger, Wagner and Mitchell	Sulfanilamide	7	57
Cawthorne	Sulfanilamide	3	66
Smith and Coon	Soluble prontosil and sulfanilamide	2	100
Sappington and Favorite	Sulfanilamide	6	67
Oarey	Sulfanilamide	4	100
Toomey and Kimball	Sulfanilamide	12	83.4
Love	Sulfanilamide and neoprontosil	1*	Recovered
Applebaum	Sulfanilamide and neoprontosil	3*	33.3
Anderson	Soluble prontosil and sulfanilamide	1	Recovered
Arnold	Sulfanilamide	1	Recovered
Smith and others	Sulfanilamide	1	Recovered

* Nonhemolytic streptococcal infections

have proved ineffective in the treatment of carriers. Some patients with cervical adenitis have improved rapidly, with cessation of fever and complete reduction in swelling, while others have shown no change and have required incision and drainage of the infected glands.

(g) Sinusitis. Good results have also been reported in cases of acute sinusitis due to hemolytic streptococci, but the results in cases of chronic sinusitis have been largely disappointing, probably because so many of the chronic conditions are due to staphylococci, pneumococci or nonhemolytic streptococci or represent mixed infections.

(h) Otitis Media and Mastoiditis. Variable and unpredictable results have been reported in cases of acute otitis media and mastoiditis. In some rapid improvement has been shown and in others, none. In still others the infection has progressed to mastoiditis, requiring operation. However, it has been observed that more prompt healing of the mastoid

wound takes place when the patient is receiving sulfanilamide, and post-operative care is shortened and simplified Maybaum, Snyder and Coleman, however, have stated that sulfanilamide may mask infections of the mastoid or render them latent and thereby add to the difficulty of diagnosis

(2) Peritonitis In cases of idiopathic streptococcic peritonitis of children, in which the mortality has varied from 54 to 100 per cent, the compound has been of value, Ladd, Botsford and Curnen reported recovery in 5 of 7 cases Stewart and Bates have also recorded recovery in 1 case

(3) Other Infections Favorable results have also been observed in cases of Ludwig's angina, streptococcic pneumonia and empyema, cellulitis and lymphadenitis and burns, as well as in cases of osteomyelitis, although sulfanilamide is usually ineffective in the presence of necrotic bone, as in chronic otitis media As reported by Lockwood and his colleagues, sulfanilamide has shown striking differences in therapeutic effectiveness against hemolytic streptococcic infections in relation to the clinical character of the infection, being most effective for septicemia, lymphangitis, erysipelas, cellulitis and early infections with little suppuration and frequently ineffective when abscesses are well established and also in wounds where the presence of debris, human or bacterial, in the form of necrotic tissue inhibits its activity In this connection, reference may be made to the observations of Bicker and Graham, who found that sulfanilamide tended to inhibit the healing of experimental uninfected wounds of dogs, which may have a bearing on the prophylactic use of the compound

Nonhemolytic Streptococci While the prontosils and sulfanilamide have usually proved ineffective in infections due to nonhemolytic streptococci, encouraging results have been reported in the treatment of ulcerative colitis, especially with neoprontosil by oral administration one hour before meals, which has been found better tolerated than sulfanilamide Unfortunately, both have usually proved ineffective in the treatment of patients with *Streptococcus viridans* endocarditis with positive blood cultures, so far as complete recovery and survival are concerned, although both, and especially sulfapyridine, have produced improvement in some instances in the way of temporarily sterile blood cultures and reduction of fever while large doses were being given I have seen 2 patients with typical symptoms and signs but with sterile blood cultures, similar to those described by Keefer, make complete recoveries after treatment with neoprontosil, but in the absence of positive blood cultures one cannot be sure that recovery may not have occurred just as well without this treatment Whether or not sulfapyridine and especially its soluble sodium salt given by intravenous

injection will prove effective remains to be determined, but the compounds are probably more hopeful and worthy of trial in cases of this highly mortal disease. All of 10 patients in my own practice treated with sulfanilamide and sulfapyridine over two to five months ultimately perished of the disease, although I thought that life was prolonged in all. At the present time interest in the treatment of this highly mortal disease with orally administered sulfapyridine combined with the intravenous administration of heparin has been greatly renewed by the encouraging report of Kelson and White.

Meningococcic Infections—That sulfanilamide protects a large percentage of mice in experimental meningococcic infections was first observed by Buttle, Gray and Stephenson and confirmed by Proom, using Miller and Castle's method of intraperitoneal inoculation in mucin

TABLE 4—*Experimental Meningococcic Septicemia*

Authors	Compounds	Treated		Controls	
		Mice, Number	Percentage of Survival	Number	Percentage of Survival
Buttle, Gray and Stephenson	Sulfanilamide	30	76.6	30	6.6
Proom	Sulfanilamide	270	84.4	270	13.7
Rosenthal	Sulfanilamide	35	31.4	35	0
Branham and Rosenthal	Sulfanilamide	265	70.6	265	8.7
Brown	Sulfanilamide	76	38.2	30	0
Bliss, Feinstein, Garrett and Long	Sulfanilamide	50	24	30	0
Bliss, Feinstein, Garrett and Long	Sulfapyridine	50	16		
McKee, Rake, Greep and Van Dyke	Sulfathiazole*	29	40	29	0
McKee, Rake, Greep and Van Dyke	Sulfapyridine	28	28.5		

* 2 (paraaminobenzenesulfonamido) thiazole

These observations were soon confirmed by Levaditi and Vaisman and others (table 4) with sulfanilamide and various derivatives. According to Brown and to Branham and Rosenthal, combined sulfanilamide and serum treatment is more effective in mice than either alone. Branham has recently reported that weight for weight sulfapyridine showed a protective action against meningococcic infections in mice about ten times that of sulfanilamide under the conditions of the experiments and that the combination of either of the two compounds with serum consistently gave results far better than those obtained with either compound alone.

Clinical reports have also shown that sulfanilamide is highly effective in the treatment of meningococcic meningitis (table 5) and is probably the compound of choice, since neoprontosil penetrates far less rapidly. Indeed, on the basis of mortality rates, the results have been equal to and in some instances decidedly better than those observed with serum treatment, and sulfapyridine may be even more effective than

sulfanilamide The optimum method of administration, however, and the indications for serum treatment in addition are not yet agreed on and must be decided according to conditions in individual cases In so far as serum is concerned, there are the questions of route and dose as well as the difficult choice of which type of serum, antitoxic or antibacterial, should be used As previously stated, experimental evidence indicates that sulfanilamide and serum are more effective than either alone, and clinical evidence is in favor of combining intravenous or intraperitoneal serum therapy with administration of the drug in cases of severe infections

But in cases of mild or average infections sulfanilamide in maximum dosage by oral administration alone appears to be sufficient when a

TABLE 5—*Meningococcic Meningitis and Chronic Septicemia*

Authors	Compounds	Number of Patients	Percentage of Recoveries
Schwenther and others	Sulfanilamide	52	85
Banks	Sulfanilamide	16	94
Banks	Sulfanilamide and sulfapyridine	72	98.6
Hobson and MacQuaide	Sulfapyridine	6	100
Jewesbury	Sulfanilamide	6	100
Eldahl	Sulfanilamide	12	75
Willen	Sulfanilamide	5	100
Somers	Sulfanilamide	143	90
Bryant	Soluble prontosil and sulfanilamide	21	95
Bryant	Sulfapyridine	168	95
Sappington and Favorite	Sulfanilamide	8	75
Muraz, Chirle and Queguiner	Sulfanilamide	54	85.2
Muraz, Chirle and Queguiner	Sulfanilamide	271	89.3
Wagelstein	Sulfanilamide	72	84.7
Dimson	Sulfapyridine	1*	Recovery
Zendel and Greenberg	Sulfanilamide	1*	Recovery

* Chronic meningococcic septicemia

concentration of at least 5 mg of free sulfanilamide per hundred cubic centimeters of spinal fluid can be secured and maintained for at least three days For comatose patients and when vomiting renders oral medication impossible parenteral administration is required Whether or not intrathecal injections of sulfanilamide are helpful in addition cannot be stated, but they are apparently worthy of trial in the treatment of severe infections, especially as a preliminary injection, and when the concentration in the spinal fluid from enteral and parenteral administration is low

Sulfanilamide and sulfapyridine are likewise indicated in the treatment of chronic meningococcic septicemia, a condition likely to be the result of persistent meningococcic infection of the nasal accessory sinuses and characterized by recurrent chills and fever, crops of cutaneous nodules, arthralgia and positive blood cultures, this disease has an unfavorable prognosis and serum treatment has generally failed

Pneumococcic Infections—Soluble prontosil was originally stated by Domagk, in 1935, to have an effect on experimental pneumococcic infections of types I and II in mice, and his results were soon confirmed

TABLE 6—*Experimental Pneumococcic Infections*

Authors	Compounds	Animals	Pneumo coccus, Types	Treated		Controls	
				Num- ber	Percent age of Survivors	Num ber	Percent age of Survivors
Rosenthal	Sulfanilamide	Rats	I, II and III	30	90	30	0
Rosenthal	Sulfanilamide	Rabbits	I	10	80	10	0
Cooper, Gross and Lewis	Sulfanilamide	Mice	II, III, VII and XXII	83	0 to 90	101	0 to 80
Cooper, Gross and Mellon	Sulfanilamide	Rats	I and III	101	20 to 80	75	0 to 45
Cooper, Gross and Mellon	Sulfapyridine	Mice	II and XXII	60	37 to 45	50	0
Rueggsegger and Ham burger	Sulfanilamide	Mice	I, II, III and VIII	212	1 to 3	129	0
Schmidt	Sulfanilamide	Mice	XIV	40	50	8	0
Whitby	Sulfanilamide	Mice	I, II, III, V, VII and VIII	667	0 to 7 days	180	97 in 33 days
Raiziss, Severac, Moet sch and Clemence	Sulfanilamide	Mice	II	45	0	80	0
Raiziss, Severac, Moet sch and Clemence	Sulfapyridine	Mice	II	50	8		
Raiziss, Severac, Moet sch and Clemence	Sulfanilamide	Mice	I, II and III	150	0 to 3		
Raiziss, Severac, Moet- sch and Clemence	Sulfapyridine	Mice	I, II and III	220	0 9 to 13 3		
Bliss, Feinstein, Gar- rett and Long	Sulfanilamide	Mice	I, II and III	125	0	75	0
Bliss, Feinstein, Gar- rett and Long	Sulfapyridine	Mice	I, II and III	125	0 8		
Kepl and Gunn	Sulfapyridine	Rats	I	81	32	57	0
Kepl and Gunn	Sulfanilamide and sulfapyridine	Rats	III	49	25	33	3
Bleter, Larson, Levine and Cranston	Sulfapyridine	Mice	II	99	44 to 63 4	100	0
Kolmer, Raiziss and Rule	Sulfanilamide	Rats	I, II and III	72	32	18	0
Kolmer, Raiziss and Rule	Sulfanilamide	Rabbits*	I, II and III	51	Effective	24	0
Kreidler	Sulfanilamide	Rabbits*	I	22	32	14	0
Larson, Bleter and Le vine	Sulfapyridine	Rabbits	II	25	76	23	4 2
Havens, Hansen and Kramer	Sulfapyridine	Rabbits	I	20	45	20	30
Gregg, Loosli and Hamburger	Sulfapyridine	Dogs†	I	24	100	32	50
McKee, Rake, Greep and Van Dyke	Sulfathiazole	Mice	I, II and III	87	20 7	60	0
McKee, Rake, Greep and Van Dyke	Sulfapyridine	Mice	I, II and III	90	44 4		

* Intradermal infections

† Pneumonia

by Horlein Subsequent studies (table 6) on pneumococcic peritonitis and septicemia of mice, intradermal infections of rabbits and pneumonia of rats and dogs have shown that sulfanilamide and especially sulfapyri-

dine are decidedly effective against many types of pneumococci, including type III, which is the only one entirely uninfluenced by serum MacLean, Rogers and Fleming recently showed that pneumococci vary in their sensitivity to sulfapyridine, and they described a test for such sensitivity, the variation is associated not with the type but with the individual strain Ross reported a case in which pneumococcic meningitis was fatal in spite of treatment with sulfapyridine, he thought that

TABLE 7—*Pneumococcic Pneumonia*

Authors	Compounds	Types	Number of Patients	Percentage of Recoveries
Evans and Galsford	Sulfapyridine	I, II, III and group IV	100	92
Finland and Brown	Sulfanilamide	I, II, V and VII	19	20 to 62.5
Price and Myers	Sulfanilamide	29 types	115	84
Traut and Logan	Sulfanilamide	Not stated	9	70
Flippin and Pepper	Sulfapyridine	I, II, III, IV, V, VI, VII and VIII	102	96 to 100
Anderson and Dowdeswell	Sulfapyridine	Various	100	95
Agranat, Dreosotl and Ordman	Sulfapyridine	Various	250	96.4
Plummer and Ensworth (a)	Sulfapyridine	Various	157	91.5
Alsted	Sulfapyridine	III	8	50
Smith and Needles	Sulfapyridine	Various	50	92
Pepper, Flippin, Schwartz and Lockwood	Sulfapyridine	I, II and III	400	93
Schwartz et al	Sulfapyridine	23 types	233	91
Plummer and Ensworth (b)	Sulfapyridine	26 types	270	87.4
Anderson, Cooper, Cairns and Brown	Sulfapyridine	II	70	91
Dowling and Abernethy	Sulfapyridine	26 types	136	89
Dowling and Abernethy	Serum	26 types	96	83.3
Nichol	Sulfapyridine	Not stated	2*	100
Barnett, Hartman, Perley and Ruhoff	Sulfanilamide	I, IV, VI, XI and XIV	43*	100
Wilson and others	Sulfapyridine	25 types	35*	Favorable
Smith and Nemir	Sulfapyridine	21 types	93*	93.5

* Infants and children

the organism had acquired a tolerance for the compound MacLeod and Daddi have succeeded in rendering a strain of type I pneumococcus "sulfapyridine fast" in vitro and in vivo, and MacLeod found the pneumococcus associated with a marked diminution in the production of hydrogen peroxide in cultures

Pneumonia While sulfanilamide has apparently been somewhat effective in the treatment of pneumococcic pneumonia there can be no doubt about the remarkable therapeutic efficacy of sulfapyridine in the treatment of lobar pneumonia and bronchopneumonia of various types in adults and in children (table 7) The first report was made by Evans and Galsford, with a mortality of 8 per cent in 100 cases, as

compared with a mortality of 27 per cent in a control group of equal size. Indeed, it appears that the mortality in adults has been lowered to between 5 to 10 per cent, and equally favorable results have been observed in children. Furthermore, if the parenteral administration of sodium sulfapyridine fulfils present expectations, the mortality is likely to be still further reduced, since blood levels of 5 to 8 mg. per hundred cubic centimeters can be attained with great speed and certainty.² Parenteral medication is advisable not only in cases in which administration of sulfapyridine by mouth is impossible or in which intestinal absorption is poor but also in cases in which prompt action of the drug is imperative, however, it should be limited to conditions in which oral administration is impossible or does not suffice for successful therapy.

A critical reduction in temperature within twenty-four to forty-eight hours has been commonly observed, generally accompanied by a diminution of toxemia and an improvement in general well-being but not usually accompanied by any significant change in the pulmonary signs. In pneumococcic empyema, however, sulfapyridine is only doubtfully effective, in spite of the fact that the compound may be found in the exudate in a concentration similar to that in the blood. The cause of this reduced therapeutic effectiveness is not understood at present, but it may be the anaerobic conditions of the closed pleural sacs.

As a result of the favorable experience with sulfapyridine, the specific treatment of pneumonia has been simplified, and the costs of treatment have been greatly reduced. But the administration of type-specific serum may be required in those instances in which the patient fails to show clinical improvement within twenty-four to thirty-six hours with adequate dosage of sulfapyridine, especially when positive blood cultures are observed. The use of serum has been advised by Finland and Brown as an adjunct in the treatment of pneumonia in patients over 40 years of age or during pregnancy or the puerperium, when treatment is begun after the third day of illness and when more than one lobe is involved. In other words, sulfapyridine renders pneumococci more susceptible to immune bodies, and the administration of type-specific immune serum is most likely required in addition to sulfapyridine in the treatment of severe infections. MacLeod, summarizing work done at the Hospital of the Rockefeller Institute of Research, expressed the opinion that such synergism exists. Groups of mice were infected with pneumococci of type III and treated, respectively, with sulfapyridine alone, serum alone and the same amount of the two agents in combination. The results showed that type III antipneumococcus serum and sulfapyridine are synergistic,

2 Marshall and Long Gailsford, Evans and Whitelaw

since amounts of each agent which used singly exerted little or no protective action afforded protection to 60 per cent of the mice when used in combination. Similar results have been reported by Powell and Jamieson in the treatment of rats infected with pneumococci of types I, II, V, VII, VIII and XV.

A combination of sulfapyridine and antipneumococcus serum accompanied by adequate supportive measures and close clinical surveillance and aided by sputum typing, blood culture, daily blood counts and urinalyses apparently offers the best prognosis in the treatment of pneumonia. Serum has ceased to be expensive, as prices have again been lowered, and when sulfapyridine is used the recommended dose of serum is reduced 50 per cent. Possibly the use of parenteral injections of sodium sulfapyridine in addition to its oral administration will still further reduce the need for supplemental serum therapy.

TABLE 8—*Experimental Pneumococcic Meningitis*

Authors	Compounds	Types	Animals	Treated		Controls	
				Num- ber	Percent age of Survivors	Num- ber	Percent age of Survivors
Kolmer, Rule and Werner	Sulfanilamide	I, II and III	Rabbits	60	0	12	0
Kolmer, Rule and Werner	Sulfanilamide	I, II and III	Monkeys	10	10	4	0
Cooper, Gross and Lewis	Sulfanilamide	II	Rats	47	50 to 73.3	36	0
Cooper, Gross and Lewis	Sulfapyridine	II	Rats	30	57	16	0
Gross, Cooper and Lewis	Sulfanilamide	II	Rats	15	59.5	37	0

Meningitis. Even more dramatic success has been observed in the treatment of pneumococcic meningitis, with which the mortality has been hitherto practically 100 per cent. In experimental pneumococcic meningitis of rabbits Kolmer, Rule and Werner found sulfanilamide ineffective, although in 10 monkeys treated there was 1 recovery. In rats, however, Cooper, Gross and Lewis and later Gross, Cooper and Lewis observed much better results with both sulfanilamide and sulfapyridine (table 8).

As shown in table 9, the use of these compounds has materially reduced the mortality from human infections, and sulfapyridine is undoubtedly the compound of choice. My personal experience is limited to 3 cases of a condition of otitic origin in which sulfapyridine was administered, with 1 recovery. Adequate and prompt surgical drainage of primary foci of infection is important when possible, along with spinal drainages at frequent intervals, and, needless to state, maximum doses of sulfapyridine are indicated in order to bring the concentration of free compound to at least 5 mg per hundred cubic

centimeters of spinal fluid In case of vomiting or semiconsciousness interfering with swallowing, intravenous injections of the soluble sodium salt are indicated, or intramuscular injections, as recommended by Cable, who used the soluble salt of M & B 693 [33½ per cent solution] Whether or not the soluble sodium salt can be safely injected intrathecally cannot be stated at the present time, but the injection of sulfanilamide by this route is indicated at the outset of treatment in order to secure effective concentrations in the spinal fluid as soon as possible

TABLE 9—*Pneumococcic Meningitis*

Authors	Compounds	Number of Patients	Percentage of Recoveries
Neal and Applebaum	Sulfanilamide	14	21
Allan, Mayer and Williams	Sulfanilamide	3	100
Hewell and Mitchell	Sulfanilamide	6	50
Finland and Brown	Sulfanilamide	10	60
Young	Sulfanilamide	1	Recovery
Cunningham	Soluble prontosil and sulfanilamide	1	Recovery
Mertins and Mertins	Soluble prontosil and sulfanilamide	1	Recovery
Latto	Soluble prontosil	1	Recovery
Barnett, Hartman, Perley and Ruboff	Sulfapyridine	3	66
Robertson	Sulfapyridine	1	Recovery
Reid and Dyke	Sulfapyridine	1	Recovery
Cutts, Gregory and West	Sulfapyridine	1	Recovery
Cable	Sodium sulfa pyridine	1	Recovery
McAlpine and Thomas	Sodium sulfa pyridine	1	Recovery
MacKeith and Oppenheimer	Sodium sulfa pyridine	5	40
Raman	Sodium sulfa pyridine	1	Recovery
Hodes, Gimbel and Burnett	Sulfapyridine and sodium sulfapyridine	17	47

Peritonitis In cases of primary pneumococcic peritonitis of infants and children, in which the mortality has varied from 65 to 100 per cent, Barnett and his colleagues have found sulfapyridine effective in the treatment of 3 patients, and Ladd and his colleagues have recorded the recovery of 2 of 3 patients treated with this compound and serum

Gonococcic Infections—While true infection of animals by gonococci is considered unattainable, Levaditi and Vaisman as well as Cohn and Peizer have observed favorable results in the treatment of experimental gonococcic peritonitis of mice with sulfanilamide, and an enthusiastic report by Dees and Colston on its use in the treatment of gonorrheal urethritis of men has been followed by a large number of

similar favorable reports (table 10), including the treatment of seminal vesiculitis, epididymitis, prostatitis, vulvovaginitis, endocervicitis and salpingitis

Almost all observers, however, record 10 to 20 per cent of patients who fail to respond, probably owing to resistant strains of gonococci, and gonorrhea is a disease in which the criteria of cure are not readily amenable to exact statement. Lich and Rowntree have recently reported that the incidence of "cure" in a free clinic practice has been only 35 per cent, with recurrences in 11 per cent of 175 cases, the duration of symptoms averaging six and eight-tenths days and varying from one to more than thirty days

TABLE 10—*Gonococcal Urethritis*

Authors	Compounds	Number of Patients	Percentage "Cured"
Dees and Colston	Sulfanilamide	47	75
Mahoney	Sulfanilamide	205	85.4
Cokkinis and McElligott	Sulfanilamide	633	80
Silver and Elliott	Sulfanilamide	1,625	Effective
Reuter	Sulfanilamide	100	90
Herrold	Sulfanilamide	30	50
Grutz	Sulfanilamide	36	66
Orean	Sulfanilamide	100	90
Ferguson, Buckholtz and Gromet	Sulfanilamide	293	76
Keefer and Rantz	Sulfanilamide	63	100
Anwyl Davies	Sulfanilamide	19	Unsatisfactory
Smith, Well and Bird	Sulfanilamide	72	87.5
Walzak	Sulfanilamide	160	12.5
Orr	Sulfanilamide	134	87
Hoffman, Schneider, Blatt and Herrold	Sulfanilamide	25*	Effective
Lich and Rowntree	Sulfanilamide	175	35
McGregor-Robertson	Sulfapyridine	201	80 to 96
Lloyd	Sulfapyridine	103	85
Prebble	Sulfapyridine	65	48 to 62.5
Bowie, Anderson, Dawson and Mackay	Sulfapyridine	97	93
Batchelor, Lees, Murrell and Braine	Sulfapyridine	70	9 to 24
Marinkovitch	Sulfapyridine	50	86
Johnson, Leberman, Pepper and Lynch	Sulfapyridine	76	80.3

* Vulvovaginitis

It is also clear that, depending on the method of treatment, a considerable number of patients may be placed in the dangerous state of being rendered symptom free or carriers of latent and residual infection. Practice in connection with irrigations and adjuvant measures varies widely, and the results to be expected in different forms of the disease are still in the process of being refined, certainly haphazard treatment is greatly to be deprecated, and the administration of adequate doses practically requires hospitalization for the best results. Furthermore, it is imperative for the laity to realize that sulfanilamide has no prophylactic value.

Some observers have expressed the opinion that treatment is more effective when begun after the acute stage is passed (Cokkinis and McElligott) and advise active immunization with vaccine for eight to ten

days before beginning treatment with the drug. The final answer to the treatment of gonorrhea in both sexes with sulfanilamide and sulfapyridine is therefore by no means solved, furthermore, with early subsidence of urethral discharge the cure and control of the disease become an increasingly formidable problem in relation to marriage and public health.

As shown in table 11, however, sulfanilamide and sulfapyridine have proved effective in the treatment of gonococcal ophthalmia and arthritis. Marvin and Wilkinson recorded the recovery of a patient

TABLE 11—*Gonococcal Ophthalmia and Arthritis*

Authors	Disease	Compounds	Number of Patients	Results
Michie	Ophthalmia	Sulfapyridine	2	Effective
Willis	Ophthalmia	Sulfanilamide	4	Effective
Barbour and Towslev	Ophthalmia	Sulfanilamide	15	Effective
Michels	Ophthalmia	Sulfanilamide	15	Effective
Fernandez and Fernandez	Ophthalmia	Sulfanilamide	8	Effective
Bruck, Hillemand and Vilde	Arthritis	Sulfanilamide	3	Effective in 2
Keefer and Rantz	Arthritis	Sulfanilamide	14	Effective

TABLE 12—*Sulfanilylsulfanilamide and Sulfanilyldimethylsulfanilamide in the Treatment of Gonococcal Urethritis*

Authors	Compounds	Number of Patients	Percentage "Cured"
Mergelsberg and Grumer	Uleron ¹	69	77
Gennrich	Uleron*	64	100
Tuhs and Volavsek	Uleron*	169	94
Willie	Uleron*	100	74
Walzak	Disulon†	36	19.4
Walzak	Disulon†	160‡	12.5
O'Crowley, James and Sutton	Disulon†	85	94
Shelley	Disulon†	100	97

* Sulfanilyldimethylsulfanilamide

† Sulfanilylsulfanilamide

‡ Treated with sulfanilamide

with gonococcal meningitis but were not inclined to give sulfanilamide the credit. In 22 cases recorded in the literature in which sulfanilamide was not administered, the mortality was 45 per cent.

While neoprontosil appears to be less effective than sulfanilamide in gonorrhea, sulfanilylsulfanilamide and sulfanilyldimethylsulfanilamide are regarded by the German physicians as superior. I have not attempted to review the extensive literature (more than 160 articles alone since 1938) but have included some of the more recent reports in table 12. It is generally recommended to delay treatment for about three weeks in order to allow the mobilization of body defenses, but it appears that the results are not superior to those observed with sulfanilamide. Furthermore these compounds are much more likely to produce

peripheral neuritis In a few cases renal or even hepatic injury has been reported as following excessive dosage or a prolonged period of administration, although it is stated that nausea, vomiting, dizziness and cyanosis are less frequently observed than with the use of sulfanilamide

Infections of the Urinary Tract—The prontosils have been used in Germany for the treatment of Bacillus coli and staphylococcic infections of the urinary tract of both adults and children, with uniform success, but there seems to be no reason for believing them to be superior or even perhaps equal to sulfanilamide for this purpose (table 13)

These compounds have been found much more bactericidal in alkaline than in acid urine As shown by Helmholtz, sulfanilamide and mandelic acid complement one another and have separate indications

TABLE 13—*Infections of the Urinary Tract*

Authors	Compounds	Patients		Results
		Num ber	Kind	
Pernice	Original prontosil	18	Children	Effective
Maraun	Original prontosil	38	Children	87 per cent cured
Meissner	Soluble prontosil	8	Adults	Effective
Clark	Sulfanilamide	Not stated	Adults	Effective
Helmholtz	Sulfanilamide	Not stated	Children	Effective
Kenny, Johnston and von Haebler	Sulfanilamide	46	Women	Effective
Cuthbert	Sulfanilamide	79	Women	Effective
Gaudin, Zide and Thompson	Sulfanilamide	100	Men	Not recommended*
Herrold	Sulfanilamide	16	Adults	75 per cent cured
Melton and Beck	Sulfapyridine	71	Adults	78 per cent cured

* After transurethral prostatectomy

The former can be given in the acute stage, acts best in alkaline urine, is effective even in the presence of renal damage, is effective in Bacillus proteus infection and is superior in the treatment of coexisting prostatitis, in some cases of which it has been demonstrated in the secretions, but it fails against Str faecalis, and about 15 per cent of patients cannot take it in sufficient dosage Mandelic acid requires highly acid urine and good renal function and is effective against Str faecalis Furthermore, mandelic acid is preferred when applicable since it is safer In other words, neoprontosil, sulfanilamide and sulfapyridine have been generally found highly effective against infections of the urinary tract due to B coli, Bacillus proteus, hemolytic streptococci and some staphylococci, but they are less effective in infections due to Str faecalis Albright, Dienes and Sulkowitch have found sulfanilamide ineffective in 2 cases of pyelonephritis with nephrocalcinosis due to Haemophilus influenzae In this connection it must be emphasized, however, that strains of B coli vary in susceptibility to sulfanilamide and that failure

in treatment may be due to infection with a strain unusually resistant both in vitro and in vivo as reported by Kolmer and Rule in 1939. This is also true of infections due to staphylococci, and under such circumstances an in vitro test for susceptibility to the compound may be of assistance in arranging dosage. Probably intravenous injection of 0.2 Gm. of neoarsphenamine twice weekly is to be preferred in the treatment of infections with unusually resistant staphylococci as, curiously, the compound is highly effective under these conditions.

Staphylococcic Infections—As previously stated, the first published report on the therapeutic use of the original prontosil was that by Foeister of the treatment of a child with staphylococcic septicemia. In fact, Domagk found this compound somewhat effective against

TABLE 14—*Experimental Staphylococcic Infections*

Author	Compound	Animal	Treated		Controls	
			Num- ber	Percent age of Survivors	Num- ber	Percent age of Survivors
Buttle	Sulfanilamide	Mice	30	50	10	0
Mellon, Shinn and McBroom	Sulfanilamide	Mice	21	38	31	14
Feinstone, Bliss, Ott and Long	Sulfanilamide	Mice	50	34	50	10
Whitby	Sulfapyridine	Mice	40	15	18	16
Whitby	Sulfapyridine	Mice	80	7.5		
Bliss and Long	Sulfanilamide	Mice	50	8	30	0
Bliss and Long	Sulfapyridine	Mice	49	33		
Barlow and Homburger	Sulfathiazole*	Mice	20	70	20	0
Barlow and Homburger	Sulfamethyl- thiazole†	Mice	20	90		
Barlow and Homburger	Sulfaphenyl- thiazole†	Mice	20	45		
Barlow and Homburger	Sulfapyridine	Mice	20	30		

* 2 (paraaminobenzenesulfonamido) thiazole

† 2 (paraaminobenzenesulfonamido) methylthiazole

experimental staphylococcic infections, and it is astonishing that since then so few clinical results have been published. I surmise, however, that this is not because both the prontosils, sulfanilamide and sulfapyridine, have failed to be employed but because the results have been so poor (especially in staphylococcic septicemia) and because failures are so seldom reported.

As shown in table 14, sulfanilamide and sulfapyridine, however, are not without some effect in the treatment of experimental staphylococcic infections of mice, and Domagk in 1937 stated that better results have been observed with ulion (sulfanilyldimethylsulfanilamide). Barlow and Homburger have found sulfamethylthiazol (2-sulfanilamidomethylthiazole, 2-[paraaminobenzene sulfonamido]-methylthiazole), a thiazole analogue of sulfapyridine prepared by Fossbinder and Walter, more effective than sulfapyridine, and this compound, as well as sulfathiazole (2-sulfanilamidothiazole, 2-[paraaminobenzene-

sulfonamido]-thiazole), is commanding special attention at present in the treatment of staphylococcic septicemia, although it is too early to express an opinion of their clinical value. These compounds (Winthrop Chemical Company) are given in doses of 5 Gm (10 tablets), followed by 1.5 Gm every four hours, day and night, for two or three days at which time each dose may be decreased and the time interval between doses lengthened in conformity with the condition of the patient. Their toxicity is low, as recently reported by Van Dyke and his colleagues.

Comparatively few successes have been reported in the treatment of staphylococcic septicemia of human beings with the prontosils, sulfanilamide and sulfapyridine (table 15), and while the literature records many failures, it is a safe assumption that a large number of such have not been recorded. At the present time sulfamethylthiazol and sulfapyridine appear to be the remedies of choice although the

TABLE 15—*Staphylococcic Septicemia*

Authors	Compounds	Number of Patients	Results
Foerster	Original prontosil	1	Recovery
Colebrook and Kenny	Sulfanilamide	3*	Two recoveries
O'Brien and McCarthy	Sulfapyridine	1	Recovery
Fenton and Hodgkiss	Sulfapyridine	1	Recovery
Wade	Sulfapyridine	1	Recovery
Abramson and Flacks	Soluble prontosil, uleronf and sulfapyridine	6	Two recoveries
Galewski	Sulfapyridine	1	Recovery
Mendell	Sulfanilamide	3	No recoveries
Thornhill, Swart and Reel	Sulfanilamide	2	Recovery

* Puerperal septicemia

† Sulfanilyldimethylsulfanilamide

chemotherapy of severe staphylococcic infections is by no means as satisfactory as that of infections due to hemolytic streptococci.

Bloch and Pacella have recorded a recovery of a patient with staphylococcic meningitis credited to sulfanilamide therapy.

Undulant Fever—It is difficult to assess the value of sulfanilamide and its derivatives in the treatment of brucellosis, because primary favorable effects may not be an index of cure in the sense of complete eradication of infection.

Comparatively little has been reported on the therapeutic activity of these compounds in the treatment of experimental brucellosis of the lower animals. Welch, Wentworth and Mickle found that the oral administration of sulfanilamide markedly increased the opsonocytaphagic activity of the serums of guinea pigs infected with *Brucella abortus*. Chinn observed that the oral administration of sulfanilamide to guinea pigs was effective in preventing generalized infections with *Br. abortus*, since cultures of the livers and spleens of treated animals subjected to

autopsy after the expiration of treatment were sterile in the majority of instances. In the guinea pigs inoculated intra-abdominally with Br abortus, *Brucella melitensis* and *Brucella suis* it was thought that complete cures were obtained in 50 to 100 per cent, the compound being less effective against Br melitensis and B1 suis than against B1 abortus. Similar results have been reported by Menefee and Poston with guinea pigs inoculated intra-abdominally with Br abortus and treated with sulfanilamide by oral administration.

TABLE 16—*Experimental Brucellosis of Mice*

Compounds	Brucella Abortus		Brucella Melitensis		Brucella Suis	
	Number of Mice	Percentage of Survivors	Number of Mice	Percentage of Survivors	Number of Mice	Percentage of Survivors
Sulfanilamide	32	37.5	32	None	16	None
Neoprontosil	32	31.2	32	25	16	None
Sulfapyridine	32	31.2	32	37.5	16	None
Dagenan*	32	25	32	25	16	None
Aldamil†	32	56.2	32	6.2	16	None
Untreated controls	32	6.2	32	None	16	None

* Sodium sulfapyridine (Merck & Co. Inc.)

† Sodium formaldehyde sulfoxylate derivative of sulfanilamide (Abbott Laboratories)

TABLE 17—*Undulant Fever*

Authors	Compounds	Number of Patients	Results
Newman	Soluble prontosil	16	Favorable
Dalyrymple Champneys	Sulfanilamide	27	24 benefited
Welch, Wentworth and Mickle	Sulfanilamide	5	Favorable
Bynum	Sulfanilamide	6	Unsatisfactory
Richardson	Soluble prontosil	2	Favorable
Francis	Soluble prontosil	2	Favorable
Punch	Soluble prontosil	1	Favorable
Toone and Jenkins	Sulfanilamide	1	Favorable
Stern and Blake	Sulfanilamide	3	Favorable
Traut and Logan	Sulfanilamide	2	Favorable
Long and Bliss	Sulfanilamide	5	Unfavorable in 4

Kolmer and Rule have used mice inoculated intra-abdominally with virulent strains of B1 abortus, Br melitensis and Br suis, with the results shown in table 16. All five of the compounds employed gave best therapeutic results in the 160 mice infected with Br abortus. Among the 160 infected with B1 melitensis, the compounds were much less effective, while in the 80 infected with B1 suis the therapeutic effects were nil in so far as survival was concerned, although all the compounds appreciably prolonged the lives of the mice, especially sulfanilamide and sulfapyridine.

As shown in table 17, the majority of clinical reports on the treatment of undulant fever in human beings have been favorable, although I believe that these refer more to the primary effects such as the relief

of fever and symptoms during the acute early stage, than to complete or biologic cure, since recurrences have frequently followed cessation of treatment. My own experience has been confined to 3 patients, in 2 of whom the condition was due to *Br. abortus* and in 1, to *Br. melitensis* (a laboratory infection). The former 2 were treated with neoprontosil, with complete recoveries, in so far as I can judge over one to three years of follow-up observation, the infection due to *Br. melitensis* was at first refractory to sulfanilamide, neoprontosil and sulfapyridine but finally yielded satisfactorily to sulfanilamide, which I believe is the compound of choice. Certainly clinical experience has taught that the primary beneficial results are not acceptable as "cure," since relapses may occur, and for this reason I advise continuing the administration of sulfanilamide in decreasing doses for at least two months after the subsidence of fever and symptoms. Only a few cases of endocarditis due to brucellosis have been recorded, but 1 in which sulfanilamide was administered by Smith and Curtis ended in failure.

TABLE 18—*Chancroid (Haemophilus of Ducey)*

Author	Compound	Number of Patients	Results
Hutchison	Sulfanilamide	11	Favorable
Hanschell	Sulfanilamide	20	Favorable
Kornblith, Jacoby and Wishengrad	Sulfanilamide	120	Favorable
Greenblatt and Sanderson	Sulfanilamide	5	Favorable

Chancroid—While I have no knowledge of the use of sulfanilamide in the treatment of experimental infections due to *Haemophilus ducroyi*, as shown in table 18, this compound has apparently proved highly effective in the treatment of chancroid and appears to be the method of choice along with local measures, since all drugs hitherto employed have proved ineffective in the management of this tedious disease which has no mortality and causes no chronic invalidism but is of high nuisance rank. Appleyard has informed me that he has observed excellent results from local applications of powdered sulfanilamide, which is interesting in relation to the effects of the compound by local applications, shortly to be discussed with more detail. Fagerstrom has also found sulfanilamide effective in the treatment of ulcerative and gangrenous balanitis.

Typhoid Fever—On the basis of results observed in the treatment of experimental *Bacillus typhosus* infections of mice (table 19), one would expect that neoprontosil, sulfanilamide and sulfapyridine might show a favorable therapeutic response in typhoid fever. But so far clinical data are too scanty to permit the expression of an opinion. According to Harries, Swyer and Thompson, sulfapyridine has an effect

on the bacteremia and fever of the disease and in general is to be regarded as of some value in treatment, but aside from these effects the evidence in favor of these compounds in treatment is still far from being convincing, although apparently worthy of further trial. Baker recorded success with the soluble prontosil in the treatment of post-typhoid urinary infection, but I can find no data bearing on the use of this and allied compounds in the treatment of typhoid carriers.

Clostridium Welchii Infections.—In 1937 Domagk found uleion (sulfamyl-dimethylsulfanilamide) sulfamylsulfanamide and sulfanilamide somewhat effective in the treatment of mice and guinea pigs inoculated with *Clostridium welchii*. As shown in table 20, Long and Bliss have found sulfanilamide and sulfapyridine highly effective in these experi-

TABLE 19—*Experimental Typhoid Infection and Typhoid Fever*

Authors	Compounds	Subject	Treated		Controls	
			Number	Results	Number	Results
Buttle, Parish, McLeod and Stephenson	Soluble prontosil	Mice	30	83% survived	20	30% survived
Kolmer and Ru'e	Sulfanilamide	Mice	22	14% survived	8	0 survived
Kolmer and Rule	Sulfapyridine	Mice	10	10% survived	4	0 survived
Schmidt	Soluble prontosil	Human beings	3	Favorable		
Diefenbach and Yuskis	Sulfanilamide	Human beings	1	Favorable		
Harkelroad	Sulfanilamide	Human beings	1	Favorable		
Coxon	Sulfapyridine	Human beings	1	Unfavorable		
Harries, Swyer and Thompson	Soluble prontosil and sulfapyridine	Human beings	7	Favorable		

mental infections. Since then the clinical results reported by Bohlman in the treatment of 3 patients in whom gas gangrene developed in spite of prophylactic antitoxin were so impressive, along with the reports of Baker and of Sadusk and Manahan in the treatment of postabortal and puerperal infections with septicemia, as to leave no doubt but that sulfanilamide and sulfapyridine are valuable adjuncts to antitoxin in the treatment of these dangerous infections.

Tuberculosis—As reported by Allison and Myers, sulfapyridine was ineffective in the treatment of 7 patients with active pulmonary tuberculosis, although it is likely that this compound, as well as neoprontosil and sulfanilamide, may be helpful in combating secondary infection of open lesions, especially infections due to hemolytic streptococci and *Staph aureus*, as indicated by the report of Weidkamp on tuberculous disease of the bone. Sappington and Favorite have found neoprontosil

and sulfanilamide ineffective in the treatment of 3 patients with tuberculous meningitis

Furthermore, the results of treatment of experimental tuberculous infections of guinea pigs and rabbits with both human and bovine strains

TABLE 20—*Clostridium Welchii* Infections

Authors	Compounds	Animal	Treated		Controls	
			Num ber	Percent age of Survivors	Num ber	Percent- age of Survivors
Long and Bliss	Sulfanilamide	Guinea pigs	64	44	41	5
Bliss, Feinstein, Garrett and Long	Sulfanilamide	Mice	40	32	40	7
Bliss, Feinstein, Garrett and Long	Sulfapyridine	Mice	40	40		
Bohlman	Sulfanilamide	Human beings	3	Recovered		
Baker	Sulfapyridine	Human beings*	1	Recovered		
Sadock and Manahan	Sulfanilamide	Human beings†	2	Recovered		

* Septicemia and peritonitis

† Postabortal

TABLE 21—*Experimental Tuberculosis*

Authors	Compounds	Animals	Treated	
			Number	Results
Rich and Follis	Sulfanilamide	Guinea pigs	31	Slightly effective
Greey, Campbell and Culley	Sulfanilamide	Guinea pigs	76	Slightly effective
Greey, Campbell and Culley	Sulfanilamide	Rabbits	10	No effect
Smithburn	Sulfanilamide	Guinea pigs	10	No effect
Kolmer, Raiziss and Rule	Sulfanilamide	Guinea pigs	30	No effect
Steinbach and Dillon	Sulfanilamide	Guinea pigs	66	No effect
Buttle and Parish	Sulfanilamide	Guinea pigs	40	Slightly effective*
Ballou and Guernon	Sulfanilamide	Guinea pigs	33	Slightly effective
Dietrich	Soluble prontosil	Guinea pigs	20	No effect
Feldman and Hinshaw	Sulfapyridine	Guinea pigs	40	Definitely effective

* With human strain, little effect in guinea pigs and none in rabbits with a bovine strain

of *Mycobacterium tuberculosis* leave one with the impression that little or nothing is to be expected in the treatment of human tuberculosis in so far as an effect on the tubercle bacillus itself is concerned, since only massive doses at best have shown inhibitory effects on experimental infections (table 21)

Miscellaneous Bacterial Diseases—As previously stated, neoprontosil and sulfanilamide have proved effective in the treatment of a high

percentage of infections of the urinary tract due to *B. coli* and *B. proteus* and these compounds as well as sulfapyridine have been found effective in the treatment of experimental infections in mice (table 22). All three have also been successfully employed in the treatment of *B. coli* septicemia and are far superior to any other chemical agent in the

TABLE 22—Miscellaneous Experimental Bacterial Infections

Authors	Compounds	Infection	Animal	Treated		Controls	
				Num ber	Percent age of Survivors	Num ber	Percent age of Survivors
Cooper, Gross and Lewis	Sulfanilamide	<i>Bacillus coli</i>	Mice	40	55		
Cooper, Gross and Lewis	Sulfapyridine	<i>Bacillus coli</i>	Mice	10	80		
Cooper, Gross and Lewis	Sulfanilamide	<i>Bacillus proteus</i>	Mice	10	80		
Cooper, Gross and Lewis	Sulfapyridine	<i>Bacillus proteus</i>	Mice	10	90		
Kolmer and Rule	Sulfanilamide	<i>Bacillus dysenteriae</i>	Mice	13	0	5	0
Buttle, Parish, McLeod and Stephenson	Sulfanilamide	<i>Bacillus friedlander</i>	Mice	70	17	40	0
Bliss, Feinstone, Garrett and Long	Sulfanilamide	<i>Bacillus friedlander</i>	Mice	45	0	30	0
Bliss, Feinstone, Garrett and Long	Sulfapyridine	<i>Bacillus friedlander</i>	Mice	45	0		
Kolmer and Rule	Sulfanilamide	<i>Bacillus friedlander</i>	Mice	32	7	8	0
Kolmer and Rule	Sulfapyridine	<i>Bacillus friedlander</i>	Mice	16	25	4	0
Cooper, Gross and Lewis	Sulfanilamide	<i>Bacillus pyocyaneus</i>	Mice	40	53		
Cooper, Gross and Lewis	Sulfapyridine	<i>Bacillus pyocyaneus</i>	Mice	20	50		
Schutze	Sulfapyridine	<i>Bacillus pestis</i>	Mice and rats	42	76	42	5
Cooper, Gross and Lewis	Sulfanilamide	<i>Bacillus pertussis</i>	Mice	60	0	20	0
Cruikshank	Sulfanilamide and sulfapyridine	<i>Bacillus anthracis</i>	Mice	120	0	30	0
May and Buck	Sulfapyridine	<i>Bacillus anthracis</i>	Mice	21	83	24	41
Campbell	Sulfapyridine	<i>Spirochaeta pallida</i>	Rabbits	7	No effect		
Porter and Hale	Sulfanilamide	<i>Listerella monocytogenes</i>	Mice	60	60	60	5
Porter and Hale	Sulfapyridine	<i>Listerella monocytogenes</i>	Mice	20	40	20	0
Porter and Hale	Sulfanilamide	<i>Erysipelothrix</i>	Mice	40	0	110	6
Porter and Hale	Sulfapyridine	<i>Erysipelothrix</i>	Mice	70	14		

treatment of this dangerous infection. My own experience has been with 5 patients with positive blood cultures, 4 of whom recovered.

On the other hand, sulfanilamide is apparently ineffective in the treatment of experimental infections of mice due to *Bacillus dysenteriae*, and reports on its effectiveness in the treatment of bacillary dysentery lack confirmation at the present time.

Sulfanilamide and especially sulfapyridine are slightly effective in the treatment of infections of mice due to Friedlander's bacillus, but

clinical reports are too few to justify an opinion of their clinical value. I have had 1 case of meningitis due to Friedlander's bacillus, secondary to suppurative ethmoiditis, in which temporary improvement was observed under treatment with sulfapyridine but the disease was fatal. A few encouraging reports have been made on the successful use of sulfapyridine in the treatment of the highly mortal pneumonia due to Fried-

TABLE 23—*Miscellaneous Bacterial Diseases*

Authors	Compounds	Disease	No of Patients	Results
Brasman and Perley	Sulfanilamide	Bacillus proteus meningitis	1	Recovered
Stewart and Bates	Sulfanilamide	Bacillus pyocyaneus (intestinal)	1	Recovered
Banks	Sulfanilamide	Bacillus pyocyaneus (intestinal)	1	Recovered
Thompson and Greenfield	Sulfanilamide	Pertussis	Not stated	Some value*
Neal and Applebaum	Sulfanilamide	Influenzal meningitis	1	Recovered
Eley	Sulfapyridine	Influenzal meningitis	2	Recovered
Roche and Caughey	Sulfapyridine	Influenzal meningitis	2	Recovered
Hamilton and Neff	Sulfapyridine	Influenzal meningitis	1	Recovered
Sappington and Favorite	Sulfanilamide	Influenzal meningitis	2	Ineffective
Meyer and Amtman	Sulfapyridine	Bacillus friedlander septicemia	1	Recovered
Swift, Moen and Hirst	Sulfanilamide	Rheumatic fever	8	Doubtful
Thomas and France	Sulfanilamide	Rheumatic fever	Few	Encouraging
Massell and Jones	Sulfanilamide	Rheumatic fever	8 (7 with chorea)	Ineffective
Coburn and Moore	Sulfanilamide	Rheumatic fever	Not stated	Some value*
Curtis	Sulfanilamide	Tularemia	1	Effective
Stannus and Findlay	Sulfapyridine	Glandular fever	1	Effective
Strickler and Stone	Sulfanilamide	Pyogenic dermatoses	12	Some value
Wilson	Sulfanilamide	Lupus erythematosus	1	Ineffective
Engels	Sulfanilamide	Lupus erythematosus	1	Ineffective
Walker	Sulfanilamide	Actinomycosis	1	Effective
Miller and Fell	Sulfanilamide	Actinomycosis	1	Effective
Poulton	Sulfanilamide	Actinomycosis	1	Effective

* In the prevention of complications

lander's bacillus, my personal experience has been with 3 patients with positive blood cultures. Of these, 2 recovered under intensive treatment with this compound, which I believe at present may be the compound of choice.

Cooper and his associates found that sulfanilamide had no therapeutic value in the treatment of experimental Bacillus pertussis infections of mice and this is likewise apparently true of pertussis of children except that this compound, as well as neoprontosil and sulfapyridine, may have some value in the prevention of the dreaded bronchopneumonia and other complications of this disease (table 23).

On the other hand, sulfanilamide and sulfapyridine have apparently proved effective in the treatment of some patients with the highly mortal *Bacillus influenzae meningitis*, especially when treatment includes the administration of adequate amounts of immune serum. I have had 3 patients, with 1 recovery, who were treated with maximum doses of neoprontosil by parenteral administration, combined with intravenous and intrathecal injections of serum.

Sulfanilamide has also proved somewhat effective in the treatment of experimental *B. pyocyaneus* infections of mice, and while clinical reports are too few to warrant an expression of its clinical value, this compound, as well as neoprontosil, appears worthy of trial in the treatment of severe infections, especially septicemia. I have had 1 patient, a child, who had septicemia with positive blood cultures but who recovered after the oral and parenteral administration of neoprontosil.

The results in acute rheumatic fever are doubtful, although it is thought that sulfanilamide may reduce or prevent the incidence of recurrence of this disease, and its administration may be worth while for this purpose.

Encouraging reports have also been made on the effectiveness of sulfanilamide in the treatment of patients with tularemia, lupus erythematosus and glandular fever. It has proved ineffective in experimental syphilis of rabbits, and Pariser has found prontosil (sulfanilamide) to exert but little effect on the reactions of the blood in seroresistant forms of this disease. Some fungi are susceptible *in vitro* but among mycotic diseases sulfanilamide has apparently proved encouraging and effective only in patients with actinomycosis, results indicating that it is probably worthy of trial in the treatment of this chronic disease.

Virus Diseases—As shown in table 24, the only experimental virus disease in which sulfanilamide and sulfapyridine have definitely proved effective is lymphogranuloma venereum in mice. As shown in table 25, these compounds have also proved highly effective in the treatment of the disease in human beings.

The curative effects of these compounds in experimental lymphocytic choriomeningitis are still doubtful, and apparently clinical reports are not available, although the tendency to spontaneous recovery renders chemotherapy hardly worth while.

In experimental encephalitis due to the St. Louis virus as well as in that due to herpetic virus and to the virus of equine encephalomyelitis, sulfanilamide has proved ineffective, and there is no reason for expecting better clinical results.

Sulfanilamide may possess some therapeutic power in experimental infections of mice with the virus of influenza, but it is doubtful if this compound, or neoprontosil or sulfapyridine has any helpful effects in

TABLE 24—*Experimental Virus and Rickettsial Infections*

Authors	Compounds	Infection	Animals	Results
MacCallum and Findlay	Sulfanilamide	Lymphogranuloma venereum	Mice	Effective
Bar	Sulfanilamide	Lymphogranuloma venereum	Mice	Effective
Levaditi	Sulfanilamide	Lymphogranuloma venereum	Mice	Effective
McKee, Rake, Greep and Van Dyke	Sulfapyridine	Lymphogranuloma venereum	Mice	Effective
McKee, Rake, Greep and Van Dyke	Sulfathiazole*	Lymphogranuloma venereum	Mice	Effective
Rosenthal	Soluble prontosil	Choriomeningitis	Mice	Effective
McKinley, Meck and Acree	Sulfanilamide	Choriomeningitis	Mice	Ineffective
McKinley, Meck and Acree	Sulfanilamide	St Louis encephalitis	Monkeys and mice	Ineffective
McKinley, Meck and Acree	Sulfanilamide	Herpetic encephalitis	Monkeys and mice	Ineffective
McKinley, Meck and Acree	Sulfanilamide	Poliomyelitis	Monkeys	Ineffective
Kelson	Sulfanilamide	Poliomyelitis	Monkeys	Ineffective
Toomey and Takacs	Sulfanilamide and sulfapyridine	Poliomyelitis	Monkeys	Ineffective
Chumenko, Crossley and Northey	Sulfanilamide	Influenza	Mice	Ineffective
Pittman	Sulfapyridine	Influenza	Mice	Effective
Cooper, Gross and Lewis	Sulfanilamide	Rabies	Rats	Slightly effective
Dochez and Slonetz	Sodium sulfanilamide	Canine distemper	Ferrets, dogs and cats	Doubtful
Dickerson and Whitnev	Sulfanilamide	Canine distemper	Dogs	Ineffective
Topping	Neoprontosil and sulfapyridine	Rocky Mountain spotted fever and endemic typhus fever	Guinea pigs	Ineffective

* 2 (paraaminobenzenesulfonamido) thiazole

TABLE 25—*Virus Diseases*

Authors	Compounds	Diseases	Number of Patients	Results
Shaffer and Arnold	Sulfanilamide	Lymphogranuloma venereum	12	Favorable
Knight and David	Sulfanilamide	Lymphogranuloma venereum	2	Favorable
Earle	Sulfapyridine	Lymphogranuloma venereum	14	Favorable
Hebb, Sullivan and Felton	Sodium sulfanilyl sulfanilate and sodium sulfanilate	Lymphogranuloma venereum	14	Favorable
Shropshear	Sulfanilamide	Lymphogranuloma venereum	10	Favorable
Young and Moore	Sulfanilamide	Influenza	5	Effective*
Thompson and Greenfield	Sulfanilamide	Measles and pertussis	Not stated	Effective*
Vigors	Sulfanilamide	Trachoma	2	Effective
Kirk, McKelvie and Russein	Sulfanilamide	Trachoma	25	Effective
Loe	Sulfanilamide	Trachoma	140	Effective
Harley, Brown and Herrell	Sulfanilamide and neoprontosil	Trachoma	11	Effective
Spearman and Vandever	Sulfapyridine	Trachoma	2	Effective
Larimer and Wiesser	Sulfanilamide	Human equine encephalitis	16	Ineffective

* In the prevention of bacterial complications

the treatment of this disease in human beings except, possibly, to reduce the incidence of complications due to secondary bacterial infection, especially with hemolytic streptococci. The same is true of the virus of measles.

Patients with trachoma, however, which is now widely regarded as a virus disease, are being successfully treated with sulfanilamide, sulfapyridine and neoprontosil. The literature records the treatment of over 300 patients with these compounds, with excellent results, especially in the early stages of the disease.

Unfortunately, the compounds have proved completely ineffective in the prophylaxis and treatment of experimental acute anterior poliomyelitis of monkeys. Rule and I have administered neoprontosil, sulfanilamide and sulfapyridine to 6 monkeys (2 for each compound) by the oral route in doses as high as 0.1 Gm. per kilogram of body weight every twelve hours for seven days in succession (first dose immediately after intracerebral inoculation), without the slightest effect, since flaccid paralysis developed in all, including 2 controls, in from seven to eleven days after inoculation. While Wagner stated the belief that sulfapyridine is worthy of clinical trial in the treatment of the disease, it is unlikely that helpful effects will be subsequently observed.

Caro has reported encouraging results in the treatment of the dreadful pemphigus with sulfanilamide, but to the best of my knowledge this compound has not generally proved effective, although Tioup and White have recently reported the successful treatment of a patient with pemphigus neonatorum with sulfapyridine, and Eiskine and Royds reported the use of the same compound in an adult with pemphigus vulgaris in whom agranulocytosis developed from the drug, the patient recovered. While the etiology is uncertain, I personally suspect that the disease is due to a virus. My experience is confined to 2 patients treated with sulfapyridine, who ultimately succumbed. It was my impression, however, that the compound reduced the degree and severity of secondary infection of the blisters with staphylococci and streptococci.

However, I have had excellent results with sulfapyridine in the treatment of 2 patients with dermatitis herpetiformis, which I also suspect may be a virus disease. After arsenic and all other measures failed, both patients promptly responded to the oral administration of the compound. At the time of writing both are kept free of the lesions by taking 10 to 20 grains (0.65 to 1.29 Gm.) per day in divided doses but as soon as medication stops the lesions return with intolerable itching. It is my hope, however, that they will ultimately recover after prolonged treatment, as the condition in each case is chronic and of three and seven years' duration, respectively.

Recently McCammon has reported that the treatment of 4 patients with smallpox with sulfanilamide gave favorable results. Whether or

not the compound is therapeutically effective against the virus cannot be stated, as the improvement noted may have been due to the prevention of secondary streptococcic and staphylococcic infection of the lesions by this drug

McKinley, Meck and Acree have found sulfanilamide ineffective in the treatment of fibromatosis and myxomatosis of rabbits, which may be due to viruses

Diseases Due to Animal Parasites—The only parasitic disease that I know of in which neoprontosil, sulfanilamide and sulfapyridine may be effective is malaria, especially in monkeys infected experimentally

TABLE 26—*Diseases Due to Animal Parasites*

Authors	Compounds	Diseases	Animals	Results
Coggeshall	Sulfanilamide	Malaria	Monkeys, canaries and chicks	Effective*
Pakenham Walsh and Rennie	Sulfanilamide and sulfapyridine	Malaria	Human beings	Effective
Diaz deLeon	Soluble prontosil	Malaria	Human beings	Effective
Hill and Goodwin	Soluble prontosil	Malaria	Human beings	Effective
Hall	Soluble prontosil and sulfanilamide	Malaria	Human beings	Ineffective
Faget, Palmer and Sherwood	Sulfanilamide	Malaria	Human beings	Ineffective
McCoy	Sulfanilamide	Trichinosis	Human beings	Ineffective
McNaught, Beard and De Eads	Sulfanilamide	Trichinosis	Rats	Slightly effective†
Brown	Sulfanilamide	Filariasis	Dogs	Ineffective
Kolmer and Rule	Sulfanilamide	Trypanosomiasis	Rats	Ineffective

* Rhesus monkeys inoculated with *Plasmodium knowlsi*, ineffective against *Plasmodium mui*, *Plasmodium cathemerium* and *Plasmodium lophurae*

† In reducing the number of encysting trichinellas by 55 per cent

with *Plasmodium knowlsi* and in human beings infected with *Plasmodium vivax* (table 26) Coggeshall has found that with mixed malarial infections in the same experimental animal sulfanilamide eradicates a virulent *P. knowlsi* infection, leaving the animal with a milder chronic *Plasmodium mui* infection. However, sulfanilamide is an inferior therapeutic agent in human malaria. Pakenham-Walsh and Rennie found sulfapyridine destructive to *P. vivax* in a patient with dementia paralytica inoculated with this parasite, and they advised against its administration during the malarial treatment of this disease.

Otherwise these compounds appear to be ineffective in the treatment of patients with trichinosis, filariasis and trypanosomiasis and most likely also with the different types of leishmaniasis.

TABLE 27—*Summary of Therapeutic Effectiveness in the Treatment of Experimental Infections*

Infections	Animals	Compounds	Results
Hemolytic streptococcus	Mice and rabbits	The prontosils, sulfanilamide and sulfapyridine	Effective
Meningococcus	Mice	Sulfanilamide, sulfapyridine and sulfathiazole*	Effective
Pneumococcus (all types)	Mice, rabbits, rats and dogs	Sulfanilamide, sulfapyridine and sulfathiazole	Effective
Gonococcus	Mice	Sulfanilamide	Effective
Staphylococcus	Mice	Sulfanilamide, sulfapyridine and sulfamethylthiazole†	Fairly effective
Brucella	Guinea pigs and mice	Neoprontosil, sulfanilamide and sulfapyridine	Effective
Bacillus typhosus	Mice	Neoprontosil, sulfanilamide and sulfapyridine	Fairly effective
Clostridium welchii	Guinea pigs and mice	Sulfanilamide and sulfapyridine	Effective
Bacillus tuberculosis	Guinea pigs and rabbits	Sulfanilamide and sulfapyridine	Doubtfully effective
Bacillus coli	Mice	Sulfanilamide and sulfapyridine	Effective
Bacillus proteus	Mice	Sulfanilamide and sulfapyridine	Effective
Bacillus dysenteriae	Mice	Sulfanilamide and sulfapyridine	Ineffective
Bacillus friedlander	Mice	Sulfanilamide and sulfapyridine	Slightly effective
Bacillus pyocyaneus	Mice	Sulfanilamide and sulfapyridine	Effective
Bacillus pertussis	Mice	Sulfanilamide	Ineffective
Bacillus pestis	Mice and rats	Sulfapyridine	Effective
Bacillus anthracis	Mice	Sulfanilamide and sulfapyridine	Doubtfully effective
Spirochaeta pallida	Rabbits	Sulfapyridine	Ineffective
Listerella monocytogenes	Mice	Sulfanilamide and sulfapyridine	Effective
Erysipelothrix	Mice	Sulfanilamide and sulfapyridine	Ineffective
Virus of lymphogranuloma venereum	Mice	Sulfanilamide, sulfapyridine and sulfathiazole*	Effective
Virus of choriomeningitis	Mice	Neoprontosil	Doubtfully effective
Virus of encephalitis	Mice and monkeys	Sulfanilamide	Ineffective
Virus of poliomyelitis	Monkeys	Sulfanilamide and sulfapyridine	Ineffective
Virus of influenza	Mice	Sulfanilamide and sulfapyridine	Ineffective
Virus of rabies	Rats	Sulfanilamide	Ineffective
Rickettsia	Guinea pigs	Neoprontosil and sulfapyridine	Ineffective
Malaria	Monkeys	Sulfanilamide and sulfapyridine	Slightly effective
Trichinosis	Rats	Sulfanilamide	Doubtfully effective
Filariasis	Dogs	Sulfanilamide	Ineffective
Trypanosomiasis	Rats	Sulfanilamide	Ineffective

* 2 (paraaminobenzenesulfonamido) thiazole

† 2 (paraaminobenzenesulfonamido) methylthiazole

Summary—In table 27 I have attempted to summarize the therapeutic effectiveness of the prontosils, sulfanilamide and sulfapyridine in the treatment of a large number of experimental infections of the lower animals, as reported on at the present time, table 28 presents a brief summary of their status in the treatment of various bacterial, virus and

TABLE 28—*Summary of Therapeutic Value in the Treatment of Human Diseases*

Diseases	Compounds	Results
Local infection of hemolytic streptococcus	Neoprontosil and sulfanilamide	Very good
Hemolytic streptococcal septicemia	Neoprontosil and sulfanilamide	Very good
Streptococcal pneumonia and empyema	Neoprontosil and sulfanilamide	Very good
Streptococcal meningitis	Neoprontosil and sulfanilamide	Good
Erysipelas	Neoprontosil and sulfanilamide	Very good
Scarlet fever	Neoprontosil and sulfanilamide	To prevent complications
Streptococcal peritonitis	Neoprontosil and sulfanilamide	Good
Streptococcus viridans endocarditis	Sulfapyridine	Worthy of use
Ulcerative colitis	Neoprontosil	Good
Meningococcal meningitis	Sulfanilamide	Very good
Meningococcal septicemia	Sulfanilamide	Worthy of use
Pneumococcal pneumonia	Sulfapyridine	Very good
Pneumococcal meningitis	Sulfapyridine	Good
Pneumococcal peritonitis	Sulfapyridine	Good
Gonococcal urethritis	Sulfanilamide and sulfapyridine	Good
Gonococcal ophthalmia	Sulfanilamide and sulfapyridine	Good
Gonococcal arthritis	Sulfanilamide and sulfapyridine	Good
Infections of the urinary tract	Neoprontosil and sulfanilamide	Good
Staphylococcal septicemia	Sulfapyridine and neoprontosil	Encouraging
Undulant fever	Sulfanilamide and neoprontosil	Good
Chancroid	Sulfanilamide	Good
Typhoid fever	Sulfanilamide	Worthy of trial
Clostridium welchii infections	Sulfanilamide, sulfapyridine and neoprontosil	Very good
Tuberculosis	Sulfanilamide	Ineffective
Bacillus pyocyaneus infections	Sulfanilamide	Worthy of use
Pertussis	Sulfanilamide	To prevent complications
Influenzal meningitis	Sulfapyridine and sulfanilamide	Worthy of use
Bacillus friedlander pneumonia	Sulfapyridine	Worthy of use
Rheumatic fever	Sulfanilamide	Doubtful
Tularemia	Sulfanilamide	Worthy of use
Glandular fever	Sulfapyridine	Worthy of use
Lupus erythematosus	Sulfanilamide	Ineffective
Pemphigus	Sulfapyridine	Encouraging
Dermatitis herpetiformis	Sulfapyridine	Worthy of use
Actinomycosis	Sulfanilamide	Worthy of use
Lymphogranuloma venereum	Sulfanilamide	Very good
Measles and pertussis	Sulfanilamide	To prevent complications
Trachoma	Sulfanilamide	Very good
Rabies	Sulfanilamide	Ineffective
Smallpox	Sulfanilamide	Doubtful
Poliomyelitis	Sulfanilamide	Ineffective
Trichinosis	Sulfanilamide	Ineffective

parasitic diseases of human beings. No one can fail to be impressed with the great and remarkable value of sulfanilamide and its derivatives in the treatment of a remarkably wide range of bacterial infections, although they are of limited value in the treatment of virus diseases and those due to animal parasites. Without doubt the discovery of the therapeutic effectiveness of sulfanilamide constitutes the greatest single triumph in therapeutic science, even outranking in importance the discovery of arsphenamine and its allied compounds for the treatment of syphilis and other diseases due to spirochetes.

It is important to mention in this connection, however, that the rational use of sulfanilamide and its derivatives is based more on bacteriologic than on clinical diagnosis, and their indiscriminate use in the absence of the former is to be deprecated. Furthermore, their value in the treatment of local infections, notably streptococcic infections of wounds and burns and suppurative infections, is probably influenced by the presence of pus and debris.

PROPHYLACTIC VALUE

That the possibilities of the prophylactic value of sulfanilamide and its derivatives are worthy of careful attention is readily appreciated. But final appraisal must depend more on the results of carefully conducted animal experiments than on clinical observations, because one cannot be sure in human beings that infection has or would have occurred. Certainly the compounds are rapidly absorbed and eliminated, so that little or nothing is to be reasonably expected from single doses. In other words, prophylaxis demands the presence of effective concentrations in the blood over at least brief periods of time. But this can be readily attained and is probably of definite prophylactic value.

Levaditi and Vaisman were first to study the prophylactic activity of the prontosils in experimental streptococcic infections of mice. Good results were observed when mice were inoculated within forty-eight hours after administration. The period of protection was found to last up to eight days. When the compounds were given parenterally, with slower absorption and elimination, protection endured for as long as twenty-three days. Montestruc observed definite prophylactic effects in rats against experimental streptococcic infections when sulfanilamide was injected in oily suspensions but not when it was given in solution. Hoare has reported that mice can be protected against intraperitoneal infection with hemolytic streptococci by the subcutaneous injection of a single dose of sulfapyridine but that repeated doses are required after infection if the compound is given by stomach. With sulfanilamide owing to its greater solubility, a single subcutaneous prophylactic injection had but little effect, but good protection was obtained when in addition to the prophylactic dose the compound was given twice daily for three days after infection. As a result of the protection afforded to mice by a single dose before infection followed by several doses thereafter and from investigations on the bactericidal power of the blood of normal human beings, Colebrook and Kenny advocated the use of sulfanilamide as a prophylactic measure in certain circumstances against hemolytic streptococcic infection in the puerperium, but they later considered that their experiments on mice had not been quite conclusive, as equally good results might have been obtained had the

initial prophylactic dose been omitted. Whitby has observed in a large number of tests in vivo and in vitro with sulfapyridine and pneumococci that the compound is not instantly bactericidal or even instantly bacteriostatic. Animals which received the compound prophylactically so that they had a high concentration in the blood at the time of intraperitoneal inoculation with pneumococci nevertheless endured blood stream invasion and multiplication which went on for some hours yet in twenty-four hours the infection was ended (the "lag" phenomenon).

As previously stated, it is difficult to judge the prophylactic value of neoprontosil, sulfanilamide and sulfapyridine on clinical grounds alone, but the following appear to be reasonable and hopeful applications:

- 1 In cases of difficult delivery and for puerperal women exposed to streptococcal infection at or near the time of delivery. However, well organized maternity units at present have an incidence of puerperal hemolytic streptococcal infections (group A) not over 1 in 500, and it would be necessary to give prophylactic treatment to thousands of women as well as to observe the equal number of untreated patients before statistical data of any real value could be obtained. But even if the compounds failed to prevent infection they would most likely prevent the rapid development of a localized infection into the more dangerous involvement of the peritoneal cavity or of the large veins draining the urogenital tract with acute or subacute septicemia.

- 2 For patients exposed to the danger of gas gangrene (*Clostridium welchii*), especially since the antitoxin is of limited prophylactic value.

- 3 In epidemics of sore throat due to milk-borne streptococci although Smith considered sulfanilamide of no prophylactic value against epidemic tonsillitis, presumably because an adequate dose could not be given indefinitely.

- 4 Possibly for the prevention of extension of hemolytic streptococcal infection to the middle ear and mastoid cells after tonsillectomy in the presence of hemolytic streptococcus, also for the prevention of extension of infection to the lateral sinus or to the meninges from the mastoid cells or nasal accessory sinuses, although, as previously stated, this has been objected to on the basis that it may mask mastoiditis secondary to otitis media.

- 5 For the prevention of peritonitis following the rupture of a suppurating vermiform appendix and from open wounds of the intestines, since these compounds are highly effective against the hemolytic streptococcus, *B. coli* and *Cl. welchii*.

- 6 For the prevention of hemolytic streptococcal infection after accidental pricking of the fingers in the necropsy or operating rooms.

- 7 For the prevention of streptococcal infections during the course of rheumatic fever, as suggested by Thomas and France and by Coburn.

and Moore who have obtained promising results with small doses of sulfanilamide given over a considerable period also for the prevention of the dreaded bronchopneumonia and otitis media due to streptococci of measles and pertussis as suggested by Thompson and Greenfield

8 For oral administration to practically all patients with rheumatic heart disease for two days before and two to three days after the extraction of infected teeth or tonsillectomy as suggested by Long and Bliss I presume this advice was given principally for whatever value sulfanilamide may have in the prevention of the dreaded and highly mortal subacute endocarditis due to *Str. viridans* but since this compound and its derivatives are but slightly effective against nonhemolytic types of streptococci I doubt if they will show this greatly to be desired prophylactic activity. However the compound given in this manner may be useful as a prophylactic measure when the foci of infection are largely or entirely due to hemolytic types of streptococci

9. For prophylaxis of meningococcic meningitis during epidemics of this disease although a distinct and important objection is the long period of time this would likely require. As previously stated sulfanilamide does not appear to have prophylactic value against gonorrhea and according to Felke the same is true of uleion (sulfanilyldimethylsulfanilamide)

The effective dose for prophylactic purposes cannot be stated at the present time. For the adult Hoare has suggested 15 grains (0.97 Gm.) of sulfanilamide or sulfapyridine every eight hours for at least three or four days pointing out that protection probably disappears twelve hours after the last dose. These appear to be sensible recommendations for infections with a short period of incubation but when longer administration is required I suggest for the adult 10 grains (0.65 Gm.) of either compound every eight hours with smaller doses for children on the basis of body weight

THERAPEUTIC VALUE OF LOCAL APPLICATIONS

If the successful therapeutic activity of sulfanilamide and its derivatives depends on their uniform permeation of infected tissues by way of the blood with the possible release or transformation into bactericidal compounds local applications would appear to be a poor alternative. For this purpose however sulfanilamide in 1 per cent solution appears to be the compound of choice since neoprontosil has much less direct action on bacteria and sulfapyridine is too low in solubility.

In the treatment of meningococcic streptococcic and pneumococcic meningitis the intrathecal injection of 10 to 30 cc. of a 1 per cent solution of sulfanilamide at the outset of treatment appears to be worthwhile in order to secure an effective concentration of free sulfanilamide in the cerebrospinal fluid as quickly as possible

J L Brown has injected the soluble prontosil into the pleural cavity in 2 cases of streptococcic empyema, with apparently good results, and Gay and Clark have shown that intrapleural injections of sulfanilamide prevent the development of an otherwise fatal streptococcic empyema in rabbits. Sulfanilamide was used locally as well as orally by Purdie and Fry for the treatment of two sinuses which had discharged pus containing streptococci for three years after parametritis. The rapid healing indicated that chronic as well as acute infections are probably amenable to local applications. Becker and Jaeger have reported good results in the treatment of various cutaneous diseases by local applications of the soluble prontosil and Schranz, in the treatment of infections of the throat by gargling with it, but theoretically a cavity in which the solution can be retained in effective concentration seems a more hopeful site than applications to the skin or mucous membrane. The use of 1 per cent solutions of sulfanilamide, however, would appear to be worthy of trial in the treatment of ocular infections due to hemolytic streptococci, pneumococci or gonococci, because of the ease of frequent applications, it may be also worthy of trial in the treatment of ethmoiditis and sphenoiditis, by instillation with the head in the Ptoetz position, as well as in the treatment of empyema, peritonitis and wounds.

MODE OF ACTION

In view of the remarkable therapeutic effectiveness of sulfanilamide and its derivatives in infections due to a wide variety of organisms, it is not surprising that considerable effort has been devoted to explaining the precise mechanism by which they produce these results. These efforts have not been alone for the purpose of improving the compounds but because they offer an approach to the mechanism of chemotherapy in general, concerning which there is little precise information.

As stated by McIntosh and Whitby, the theories advanced from time to time may be grouped under the following four heads: (1) that the compounds have a stimulating action on the specific and nonspecific body defenses, (2) that they are capable of neutralizing toxic bacterial products, (3) that they act on bacteria themselves, either as germicides or, in some more subtle fashion, by interfering with invasive power and ability to multiply rapidly, or (4) that they act by some combination of two or more of these mechanisms.

There is, however, little evidence to support the hypothesis that they directly stimulate the specific and nonspecific body defenses. Disposal of organisms exposed to sulfanilamide *in vitro* and *in vivo* by phagocytosis has been commonly observed, but it is doubtful if this is due to a direct stimulating effect on leukocytes, as suggested by Tunnicliffe. Nor is there any evidence to show that they stimulate the antibody-

producing tissues, with the increased production of such normal or acquired specific antibodies as antitoxins, opsonins, agglutinins and bacteriolysins or such nonspecific substances as leukins and plakins. Nor is there any evidence to support the original hypothesis of Levaditi and Vaisman that they prevent the formation of capsules or destroy those that have been produced.

Furthermore, it is doubtful if they are capable of inactivating exotoxins or endotoxins, although Carpenter and Barbour have recently reported that sulfanilamide protected 87.7 per cent of 80 mice against streptococcus toxin, 84 per cent of 100 against *Cl. welchii* toxin, 86.7 per cent of 60 against *Clostridium botulinum* toxin but only 5 per cent of 60 against the toxin of the gonococcus.

But sulfanilamide may prevent the formation of toxins, as suggested by Osgood and Powell. Gay and Clark have observed that under certain conditions it acts on the streptococcus not only by inhibiting growth but by temporarily inhibiting hemotoxin formation, without being able to neutralize hemotoxin already formed. No significant effect, however, was found on the formation of leukocidin or fibrinolysin.

On the other hand, all the available evidence indicates that sulfanilamide and its derivatives inhibit the growth of streptococci and other organisms both in vitro and in vivo, as shown by Keefe and Rantz and by others. The degree of bacteriostasis in vitro is, of course, in relation to the culture medium, if it is poor, bacteriostasis is marked and may even result in complete sterilization, and if it is good, complete destruction of even small numbers of bacteria does not occur. As shown by King, Henschell and Green, sulfanilamide inhibits beta streptococci in tissue cultures, the effects varying directly with the concentration of the compound and inversely with the number of colonies, reduction in hemolysis was observed to accompany bacteriostasis. Stamp has extracted a fraction from a broth culture of group C hemolytic streptococci which is capable of antagonizing the bacteriostatic action of sulfanilamide and sulfapyridine in vitro and apparently free from protein and consists of a mixture of substances of relatively low molecular weight including free amino acids.

The important question is how sulfanilamide and its derivatives produce bacteriostasis. Available evidence indicates that it is probably the result of neutralization or inactivation of some metabolic or enzymatic activity on the part of the organisms. For this reason the observations of Shinn, Main and Mellon indicating that pneumococci and streptococci may convert sulfanilamide into an anticatalytic compound capable of inactivating blood catalase and thereby allowing the accumulation of hydrogen peroxide, which is destructive for these organisms, command attention, as does the observation by Lockwood that the compound destroys proteases and thereby inhibits bacterial

growth Also of interest is the theory of Mellon, of Buttle and his associates and of Domagk that the compound interacts with the tissues reciprocally by a process of potentiation resulting in bacteriostasis

In other words, it appears at the present time that the therapeutic efficacy of sulfanilamide and its derivatives depends on their ability to inhibit the growth of organisms both *in vitro* and *in vivo* by interfering with their proliferative activities probably by affecting the metabolic and enzymatic activity This naturally reduces their invasiveness *in vivo*, and under the conditions the organisms reduced in numbers are thereby better and more promptly removed by phagocytosis by leukocytes and the cells of the reticuloendothelial system, as well as possibly directly destroyed by natural or acquired bacteriolysins and by such natural nonspecific immune bodies as the leukins and plakins of the blood In other words, inhibition of growth (bacteriostasis) appears to be the important primary effect, and disposal of the organisms by phagocytosis appears to be the important secondary effect In this respect sulfanilamide and its derivatives act like "chemical opsonins," in the sense that the organism is first rendered vulnerable or susceptible to phagocytosis by them, as shown by Chandler and Janeway, by Kolmer, Rule and Werner, by Reid and by others

For a discussion of the relation of chemical constitution to chemotherapeutic action, I can do no better than to quote from Marshall

Two lines of research which are being pursued actively at present have for their objectives 1, to obtain more effective and less toxic drugs to use in place of sulfanilamide, and 2, to obtain drugs which are effective in bacterial infections in which sulfanilamide fails Since many hundreds of compounds have already been tested, we can study to a limited extent the important problem of the relation of chemical constitution to effective chemotherapeutic action In general only qualitative conclusions can be drawn, because few comparisons of the effectiveness of different compounds have been made in a really quantitative manner, the number of mice used is frequently too small and, due to differences in absorption and excretion, the doses used do not express the correct relation between the compounds A comparison of compounds on the basis of the blood concentration necessary for a given therapeutic effect would be much more valuable Another difficulty is the lack of a standard method for assaying the therapeutic value of new compounds The strain of organism, the virulence and number of organisms used for infection, the amount and spacing of the dosage, the time after infection or administering the first dose, the length of the period of therapy, and the length of time the mice are observed unquestionably affect the quantitative comparison of two active compounds having different ratios of absorption and excretion The two general methods in use for assaying a new compound are to compare the compound with sulfanilamide on the basis of average survival time of the treated mice or to compare the mortality rates of groups of mice treated with the compound and with sulfanilamide, these two methods probably do not give the same result with all compounds

So far, all of these newer compounds which have been shown to be active against bacterial infections contain sulfur It has been demonstrated, however,

that the sulfonamide group is not necessary for activity. Many compounds which do not contain this group and cannot yield it in the body are highly effective as bacterial chemotherapeutic agents. Thus mercaptans, disulfides, sulfinic acids, sulfonic acids, monosulfides, sulfoxides, and sulfones containing an aromatic nucleus have all been reported to have definite therapeutic activity against streptococcus infection in mice. With few exceptions, all of these compounds which are active contain a nitro, amino, or substituted amino group in the para-position to the sulfur.

Considerable information is available concerning the effect of changes in the sulfanilamide molecule on antistreptococcus activity. Little or no activity is found in mononuclear compounds in which either the amino group is replaced by some other group or the sulfonamide group by groups not yielding a sulfonic acid on oxidation. An apparent exception to this is the activity of compounds where the amino group is replaced by a nitro group or azo linkage. This is to be explained by the ready change of such compounds to an amino compound in the organism. A shift of the amino group to the ortho or meta position results in loss of activity, also, a third group in the benzene ring results in loss or lowering of activity. Substitution of amino group by alkyl, aralkyl, substituted alkyl or aryl, acyl, and alkylidene groups in general results in lowering or loss of activity. However, substitution on the amide nitrogen has a variable effect. Methyl and ethyl groups have little effect, higher alkyl groups decrease the activity, and p-amino- or p-nitrophenyl groups are stated to increase it. Compounds of the type of sulfanilyl-sulfanilamide (or polycyclic chains of the same general type) have been found active, while with substituents in the parent ring the highest activity is found in the para-derivative, carboxy or sulfonic acid groups in the ortho position in the second ring give the greatest activity. Derivatives of the true disulfanilamide type have been stated recently to be active.

The question of whether or not a real specificity for different organisms exists cannot be answered dogmatically at present. The difference in activity of various compounds against organisms like streptococci, pneumococci and gonococci may be a quantitative rather than a qualitative difference. The fact that diaminodiphenyl-sulfone and 2-sulfanilylaminopyridine are both effective against streptococcus infections, but infinitely more effective against pneumococcus than sulfanilamide, would argue for some sort of specificity, as would the limited data available on the treatment of experimental virus infections.

ABSORPTION, EXCRETION AND DISTRIBUTION

In human beings sulfanilamide is nearly completely absorbed in three to four hours after oral ingestion of moderate doses in capsules or tablets (Marshall), the same is true of neoprontosil, sulfapyridine, sulfanilylsulfanilamide and sulfanilyldimethylsulfanilamide. Sulfanilamide is absorbed much more quickly when taken in solution by mouth than when taken in solid form, apparently because the drug is rapidly absorbed from the intestine (Marshall). Absorption of solutions of sulfanilamide and neoprontosil from the subcutaneous tissues and muscles is even more rapid, and consequently parenteral administration is frequently indicated for the initial dose in severe infections.

After absorption a portion of sulfanilamide is conjugated in the liver (Harris and Klein) into acetylsulfanilamide (the paraacetylamino

derivative of benzenesulfonamide), which is practically inactive against streptococci in mice, with sulfapyridine acetylation is roughly constant for an individual subject and varies widely around 60 per cent in human beings (Long and Feinstein). Both are excreted in the urine partly in the free form and partly as the conjugated compound. Only a small amount is usually unaccounted for in human beings.

The excretion of both free and acetylated compounds occurs mostly in the urine and is rapid (twenty-four and forty-eight hours), similar to that of urea, but reabsorption by the tubules occurs to a greater extent. Elimination is reduced in nephritis with deficient nitrogen excretion, so that greater care is required in dosage in the presence of nephritis. The clearance, however, is definitely increased by an increased rate of flow of urine,³ which is of some importance in the treatment of gonorrhea and of infections of the urinary tract, in relation to fluid intake. And, as shown by Stewart, Rourke and Allen, precipitation of excreted sulfanilamide in urine at room temperature suggests the possibility of the formation of stones in the urinary tract should the volume of urine become too small during sulfanilamide therapy.

Sulfanilamide resembles urea and ethyl alcohol in its equal distribution in the body, it apparently diffuses readily to all tissues and fluids. This, however, is in relation to vascular supply, so that diffusion in areas of chronic infection, bone and necrotic tissues may be deficient and thus explain deficient therapeutic activity. It is present in saliva (Fickling, Pincus and Boyd-Cooper), pancreatic juice, bile, exudates and transudates in a concentration slightly lower than in blood and readily passes into the cerebrospinal fluid (Marshall). As might be expected, it passes from the maternal to the fetal circulation in pregnant animals and women and is present in the same concentration in the fetal and in the maternal blood.⁴ It has produced abortion in rabbits and should be given cautiously during pregnancy. It has been found in human milk⁵ in the same concentration as in the blood, or in a higher concentration, but with apparently no toxic effects on nursing infants.

DOSAGE AND ADMINISTRATION

On the basis of rate of absorption and elimination, of the concentration of free sulfanilamide required in the blood for therapeutic effectiveness and of the results of the treatment of experimental infections and human disease, the following principles in dosage and administration of sulfanilamide and its important derivatives appear warranted.

1 Treatment should be begun as soon as possible and preferably after bacteriologic as well as clinical diagnosis has been made.

3 Marshall, Stokinger, Bar.

4 Barker, Lee, Anderson and Chen, Speert.

5 Adair, Hesseltine and Hac, Stewart and Pratt.

2 A large initial dose is indicated, especially in severe or moderately severe infections, in order to produce an effective concentration of free sulfanilamide in the blood as soon as possible. In other words, the principle involved is exactly the same as in serum therapy, namely, to bring about an effective concentration in the blood as quickly as possible.

3 The chosen compound should be given orally when possible. Otherwise an 0.8 to 1 per cent solution of sulfanilamide may be given subcutaneously, intramuscularly or intravenously, or a 5 per cent solution of neoprontosil may be given intramuscularly. A 25 per cent suspension of sulfapyridine in sterile olive oil has been used intramuscularly but may produce marked local reactions. A soluble sodium salt of sulfapyridine (Meick & Co., Inc.) is being used at present by intravenous injection but at the time of writing is not available for general use. The adult dose is ordinarily 1 Gm dissolved in 25 cc of saline solution. It should be injected slowly. Accidental perivascular injections produce painful reactions. In England the May and Bell Company have produced a soluble sodium salt (M & B soluble 693) dispensed in a dose of 1 Gm dissolved in 3 cc of water for intramuscular (not subcutaneous) injection. It is reported as being not unduly painful and less toxic, with the production of less nausea and vomiting than are caused by the insoluble sulfapyridine by oral administration.

4 Parenteral administration is sometimes preferred for the initial dose and may be required for comatose patients or persons whose vomiting prevents oral administration.

5 The compound should be given every four to six hours day and night for at least several days until improvement occurs, in order to maintain an effective level in the blood and tissues.

6 The concentration of free sulfanilamide and sulfapyridine in the blood varies considerably in different persons, probably in relation to absorption from the gastrointestinal tract. For this reason tests for concentration in the blood are always advisable at frequent intervals for the purpose of adjusting dosage. For this purpose 5 cc of blood should be removed from a vein about four hours after the preceding dose.

7 For severe infections the dose of sulfanilamide should be such as to maintain a level of free sulfanilamide of 10 to 15 mg per hundred cubic centimeters of blood (table 29), for sulfapyridine a level of about 5 mg per hundred cubic centimeters appears sufficient.

8 For moderately severe infections a level of 5 to 10 mg of free sulfanilamide per hundred cubic centimeters of blood appears sufficient (table 30).

TABLE 29 —*Dosage of Sulfanilamide for the Treatment of Severe Infections*

Weight		First Dose		Every Four Hours*		Total, First Twenty Four Hours		Daily Maintenance Dose†	
Pounds	Kilograms	Grains	Grams	Grains	Grams	Grains	Grams	Grains	Grams
25	11.3	30	1.9	5	0.3	55	3.5	30	1.9
50	22.7	50	3.2	10	0.65	100	6.5	60	3.9
75	34 to 45.4	60	3.9	15	1.0	135	8.7	90	5.8
125	56.7	70	4.5	15	1.0	145	9.4	90	5.8
150	68.0	80	5.2	20	1.3	200	13.0	120	7.8

1 These doses are usually required for establishing a level of 10 to 15 mg per hundred cubic centimeters of blood

2 Calculate dosage according to body weight

3 Give large initial dose, followed by maintenance dose every four hours

4 The total daily dose is approximately 1 grain per pound (0.13 Gm per kilogram) of body weight

5 Give $\frac{1}{2}$ grain (0.03 Gm) of sodium bicarbonate with each grain (0.06 Gm) of sulfanilamide orally

* Day and night

† Usually for two to six days reduce when improvement occurs

TABLE 30 —*Dosage of Sulfanilamide for the Treatment of Moderately Severe Infections*

Weight		Orally, Every Four Hours*		Total, Twenty Four Hours†	
Pounds	Kilograms	Grains	Grams	Grains	Grams
25	11.3	5	0.3	30	1.9
50	22.7	10	0.65	60	3.9
75 to 100	34.0 to 45.4	10	0.65	60	3.9
125	56.7	15	1.0	90	5.8
150	68.0	15	1.0	90	5.8

1 These doses are usually required for establishing a level of 5 to 10 mg per hundred cubic centimeters of blood

2 Calculate total amount required per day, divide into six parts and give dose every four hours

3 The total daily dose is approximately $\frac{1}{2}$ grain per pound (0.066 Gm per kilogram) of body weight

4 Give $\frac{1}{2}$ grain (0.03 Gm) of sodium bicarbonate with each grain (0.06 Gm) of sulfanilamide orally

* Day and night

† Usually for two to four days, reduce when improvement occurs

TABLE 31 —*Dosage of Sulfanilamide for the Treatment of Mild Infections*

Weight		Orally, Every Four to Six Hours*		Total, Twenty Four Hours	
Pounds	Kilograms	Grains	Grams	Grains	Grams
25	11.3	2½	0.16	15	1.0
50	22.7	5	0.3	15	1.0
75 to 100	34.0 to 45.4	5	0.3	30	1.9
125	56.7	10	0.65	30	1.9
150	68.0	10	0.65	45	2.9

1 Calculate total amount required per day, give dose every four hours for several days and then every six hours

2 Give $\frac{1}{2}$ grain (0.03 Gm) of sodium bicarbonate with each grain (0.06 Gm) of sulfanilamide orally

* Preferably day and night

9 For mild infections determinations of the concentration in the blood are not ordinarily required (table 31)

10 For severe infections and in the treatment of patients who cannot swallow or if vomiting interferes with oral administration, parenteral administration of sulfanilamide or neoprontosil is required (table 32)

11 It is frequently advisable to give the drug orally and parenterally, especially in the treatment of severe infections (table 33)

TABLE 32—*Dosage of Sulfanilamide and Neoprontosil for Parenteral Administration*

Infection	1% Solution of Sulfanilamide			5% Solution of Neoprontosil		
	Per Lb *	Total in 24 Hrs per Lb	Equivalent per 150 Lbs in 24 Hrs	Per Lb *	Total in 24 Hrs per Lb	Equivalent per 150 Lbs in 24 Hrs
Very severe	1 cc	4 cc	600 cc (6 Gm)	0.2 cc	0.8 cc	120 cc (6 Gm)
Moderately severe	0.6 cc	2.5 cc	400 cc (4 Gm)	0.1 cc	0.5 cc	80 cc (4 Gm)

1 This method of administration is to be used in case of vomiting or inability to swallow (comatose state)

2 A 1 per cent solution of sulfanilamide may be used (subcutaneously or intravenously) or a 5 per cent solution of neoprontosil (subcutaneously or intramuscularly)

* Every six hours

TABLE 33—*Dosage of Sulfanilamide and Neoprontosil for Combined Oral and Parenteral Administration*

Infection	Total Dose per 20 Lbs in 24 Hrs	Oral Dose per 20 Lbs Every 4 Hrs	Parenteral Dose per 20 Lbs Every 12 Hrs	
			1 per Cent Sulfanilamide	5 per Cent Neoprontosil
Very severe	1.2 Gm (20 gr)	0.1 Gm	20 cc or →	6 cc
Moderately severe	0.8 Gm (12 gr)	0.1 Gm	10 cc or →	2 cc

1 This method is always advisable for the first two to six days in severe infections

2 It may be continued until convalescence is established if full dose cannot be given orally

3 Give oral doses every four hours and parenteral doses every twelve hours

12 Intraspinal injections of 0.8 to 1 per cent solutions of sulfanilamide are sometimes advisable at the beginning of the treatment of patients with pneumococcic, streptococcic, influenzal and severe meningococcic meningitis, in order to secure an effective concentration in the cerebrospinal fluid as soon as possible. The amount or volume is the same as that of immune serums.

13 When improvement occurs the total daily dose is reduced or the intervals of administration lengthened, but treatment should be continued if possible until convalescence is well established and cultures are negative, to prevent recrudescence of infection.

14 It is highly probable, however, that organisms may acquire a tolerance for any of the sulfonamide compounds and whenever resump-

tion of treatment is required it appears preferable to choose another of those available

15 Apparently sulfanilamide and allied compounds render bacteria more susceptible to immune bodies, and therefore it appears that serum therapy should be used at the same time, especially in the treatment of patients with severe pneumonia or pneumococcic, meningococcic or influenzal meningitis. Blood transfusions and active immunization with vaccines are also helpful in some infections. In other words, it appears advisable not to forego anything of value in surgical drainage, serum and vaccine therapy and transfusion in the treatment of severe infections but to use chemotherapy with these compounds as important adjuvants to treatment.

TABLE 34—*Dosage of Sulfapyridine for the Treatment of Pneumonia*

Patients	Dosage
Children	Orally 1 to 1½ gr per pound (0.13 to 0.2 Gm per kilogram) of body weight each twenty four hours, divided into six doses
Adults	Initial dose orally 2 Gm (31 gr), then 1 Gm (15 gr) every four hours for a total of 25 Gm* Intravenously † 1 Gm of sodium sulfapyridine dissolved in 25 cc of saline solution every four to six hours Intramuscularly † 1 Gm of sodium sulfapyridine dissolved in 3 cc of water every four to six hours

* Except when treatment is started on or after fifth day (total 15 Gm)

† For children less according to age and weight. Especially advisable in the treatment of patients with pneumococcic meningitis

16 The incompatibilities with other drugs are not well understood at the present time. When sulfanilamide, neoprontosil, sulfapyridine and sulfanilyldimethylsulfanilamide are given orally it is generally advised to avoid the administration of other drugs, but I believe the importance of this has been greatly overrated. Patients should avoid exposure to sunlight or to ultraviolet rays from a lamp while receiving sulfanilamide therapy, because photosensitization appears to predispose to dermatitis.

17 In infections of the urinary tract it is desirable to restrict fluids until the specific gravity of the urine is 1.020 or higher and to give an alkaline diet and alkalis to maintain an alkaline reaction in the urine.

18 Suggested doses of sulfapyridine in the treatment of pneumonia are given in table 34. The dose of sodium sulfapyridine by intravenous injection is about 1 Gm dissolved in 25 cc of saline solution every four to six hours by slow injection. Accidental perivascular injections produce severe reactions.

19 The doses of sulfanilamide in the treatment of gonorrheal infections are shown in table 35. The dose of sulfanilyldimethylsulfanilamide for adults is 3 Gm daily for four consecutive days, or 4 Gm daily for three consecutive days in divided doses. The total dose for one course of treatment should not exceed 12 Gm. After each course of treatment there should be an interval of seven days during which no sulfonamide medication is given. A maximum of three courses of treatment with sulfanilyldimethylsulfanilamide orally or its sodium salt intravenously should not be exceeded.

20 Watch carefully for evidences of toxicity. The patient should not be allowed to drive a car or to pursue any occupation in which temporary mental confusion or lapse in judgment would be dangerous. The skin should be watched daily for rashes, and the temperature

TABLE 35—*Dosage of Sulfanilamide for the Treatment of Gonococcic Infections*

Days	Ambulatory Patients Orally, Every Six Hours*	Hospitalized Patients		
		Orally, Every Six Hours*	Neoprontosil, 10 Cc Dose	Orally, Every Four Hours
First two	1.3 Gm (20 gr)	0.65 Gm (10 gr)	Every six hours	1.2 Gm (16 gr)
Next five	1.0 Gm (15 gr)	0.65 Gm (10 gr)	Every eight hours	1.0 Gm (15 gr)
Next ten	0.65 Gm (10 gr)	0.65 Gm (10 gr)	Every twelve hours	Reduced dosage
Next fourteen	0.32 Gm (5 gr)	0.32 Gm (5 gr)	Once daily	

1 There is no unanimity of opinion as to the value of this method.

2 The results are better if the patient is hospitalized.

3 A longer period of treatment is required in females than in males.

* Preferably day and night.

should be recorded for evidences of drug fever. A decision as to whether the compound should be discontinued must depend on the severity of the infection and the degree of reaction. The hemoglobin, erythrocyte and leukocyte estimations should be checked at frequent intervals for hemolytic anemia and neutropenia. Treatment should be stopped if marked reductions occur which are not explainable by other factors.

TOXICITY

Sulfonamide compounds were used in human beings before much was known of their toxicity, pharmacologic or pathologic effects in animals. And while it is too well known to merit comment that chemical compounds may produce toxic effects in human beings which cannot be detected in animal tests, the value of such tests is well known in relation to chemotherapy.

As shown in table 36, the minimal lethal dose of sulfanilamide for mice by oral administration is around 4 Gm per kilogram. The max-

TABLE 36—*Toxicity in Animals*

Compound	Author	Maximum Dose Tolerated, per Kilogram Body Weight			Minimum Lethal Dose, per Kilogram Body Weight		
		Mice	Rats	Rabbits	Mice	Rats	Rabbits
Sulfanilamide	Raiziss, Severac, Moetsch and Clemence	2.0 Gm (subcutane- ously)	0.4 Gm + (intraven- ously)	1.5 Gm (orally) 0.2 Gm + (intraven- ously)			
Sulfanilamide	Montestrué				4.8 Gm (orally)		
Sulfanilamide	Fenstone, Bliss, Ott and Long				3.3 Gm (orally)		
Sulfanilamide	Marshall				3.8 Gm (orally)		
Soluble protosil	Raiziss, Severac, Moetsch and Clemence (1937)		1.0 Gm + (intraven- ously)				0.1 Gm + (intraven- ously)
Sulfapyridine	Wien				1.2 Gm (orally)		
Uleron*	Winthrop Chemical Co., Inc	2.0 Gm (orally)	2.0 Gm (orally)	5.0 Gm (orally)	10.0 Gm + (orally)		
Sodium salt of uleron*	Winthrop Chemical Co., Inc	2.25 Gm (subcutane- ously)	2.25 Gm (intramus- cularly)		16.0 Gm (orally)	13.0 Gm (orally)	0.25 Gm (intraven- ously)
Sodium salt of uleron*	Winthrop Chemical Co., Inc	9.0 Gm (orally)			3.0 Gm (intramus- cularly)	3.0 Gm (intramus- cularly)	

* Sulfanilydimethylsulfanilamide

imum tolerated dose is about half this amount. The toxicity of sulfapyridine is about the same, sulfanilyldimethylsulfanilamide is apparently less toxic. The rat is thought to be more susceptible than the mouse, and the rabbit is definitely so, as the minimal lethal dose by oral administration is between 2 and 3 Gm per kilogram of body weight. Dogs appear to be more resistant, while guinea pigs appear to be even more susceptible than rabbits. Little information is available on the toxic effects of repeated doses, but it is apparent that neoprontosil, sulfanilamide, sulfapyridine and sulfanilyldimethylsulfanilamide are remarkably low in toxicity for the lower animals.

TABLE 37—*Toxic Manifestations*

Manifestations	Frequency	Significance
Dizziness, depression, disorientation	Common	Requires caution in ambulatory patients
Anorexia and nausea	Common	Seldom requires stopping treatment
Vomiting*, acidosis	2 to 5%	Usually prevented by administration of alkalis; may require parenteral administration
Cyanosis	Common	Of little clinical significance
Drug fever	3 to 9%	May be forerunner of hemolytic anemia or agranulocytosis, stop treatment
Dermatitis	1 to 3%	Best to stop treatment temporarily if not urgently required
Mild hemolytic anemia	Common	Not dangerous, watch carefully, treatment may continue
Severe hemolytic anemia	2 to 4% adults 8 to 10% children	Dangerous, stop treatment or continue with transfusions
Transient neutropenia	40 to 50%	Treatment may continue, but watch carefully
Agranulocytosis	Uncommon	Very dangerous, over 80% mortality rate; stop treatment
Toxic hepatitis	Rare	Stop treatment
Hematuria and uroliths*	Infrequent	Stop or reduce treatment, cautious dosage in cases of nephritis
Porphyrimuria	Infrequent	Caution in dosage
Peripheral neuritis†	Uncommon	Stop treatment
Inhibition of spermatogenesis	Doubtful	No significance

* Particularly likely to occur after the use of sulfapyridine

† Particularly likely to occur after the use of sulfanilyldimethylsulfanilamide

Hawking has described in cats which died from large doses certain degenerative changes in the spinal cord and brain, and similar changes have been reported in dogs along with acidosis from large doses (Marshall). Similar changes have not been observed in human beings, although the sulfonamides commonly produce cerebral toxic effects of minor degree and likewise polyneuritis in some instances. Contrary to all other observers, Davis, Hallis and Schmeisser reported pathologic changes in the liver, kidney, spleen and lung from the administration of the compounds to rats. Hageman reported that sulfanilamide and soluble prontosil had no effect on the liver and kidneys of mice but produced hemosiderosis of the spleen and an increase of eosinophils in the bone marrow. Nelson has also reported histologic changes in various organs of rabbits and hens produced by sulfanilamide and sulfanilylsulfanilamide in doses of 0.5 to 1 Gm of the former and 1 Gm of the latter per kilogram of body weight per day.

The toxic manifestations which may occur in human beings are summarized in table 37, along with their frequency, as based on various reports, and their probable significance

1 *Mental Symptoms*—It is rather common for ambulatory patients to complain of dizziness, depression, disorientation and decreased mental acuity, especially when large amounts of the drugs are ingested. Judgment may be impaired, and for this reason caution is required on the part of those driving automobiles or engaged in hazardous occupations, and alcohol should be forbidden, as it tends to accentuate these cerebral toxic manifestations

2 *Anorexia*—Anorexia is likewise a common complaint but rarely severe enough to stop treatment

3 *Nausea and Vomiting*—Nausea and vomiting may occur in a small percentage of patients, especially after the administration of sulfapyridine. This is commonly thought to be due to acidosis with loss of sodium potassium, and for this reason it is generally advised to administer sodium bicarbonate with each oral dose. On the other hand, nausea and vomiting may be due to disturbances of the vomiting center, especially after intravenous injections of sodium sulfapyridine. Some physicians are of the opinion that daily doses of 0.3 Gm of ascorbic acid in tablets may effectually alleviate or prevent these reactions

4 *Acidosis*—An explanation of the acidosis and alkalinity of the urine has been offered by Marshall and Walzl, who have shown that 70 to 80 per cent of sulfanilamide in the glomerular filtrate is reabsorbed in the tubules, which may interfere with the reabsorption of bicarbonate and base. Hartman, Perley and Barnett, however, have demonstrated that although the alkali reserve falls and bicarbonate is excreted in the urine, the p_H of the serum remains constant or even rises, and they have stated the belief that the fall in alkali reserve is an attempt to compensate for a gaseous alkalosis due to hyperpnea. In other words if this is true, the hyperpnea is primary, possibly through central effect on the Hering-Breuer reflex, with a compensatory fall in alkali reserve

5 *Cyanosis*—Some degree of cyanosis is commonly observed which may become so pronounced as to alarm both patient and family, so it is always wise for the physician to explain the possibility of its occurrence and harmlessness, as it is otherwise of little clinical significance. It is commonly thought to be due to sulfhemoglobinemia, which Archer and Discombe explained was due to catalysis by sulfanilamide of the reaction between hydrogen sulfide and hemoglobin, measures for preventing it are directed to preventing the absorption of hydrogen sulfide from the intestines and include a low residue diet without eggs and the avoidance of all purgatives (especially magnesium sulfate) except liquid petrolatum

Others have thought that the cyanosis was due to methemoglobinemia (Paton and Eaton), and the intravenous injection of 0.3 to 0.5 Gm of methylthionine chloride (methylene blue) or the oral administration of 1 Gm every four hours was originally advised by Hauschild and has since been favorably reported on by Wendel, by Haitman, Perley and Burnett and by Campbell and Morgan, on the basis of converting methemoglobin into hemoglobin. According to Campbell and Morgan, however, it has no effect on the cyanosis due to sulfapyridine. Marshall and Walzl have offered evidence to show that cyanosis may sometimes be due to a cause other than the formation of either methemoglobin or sulfhemoglobin. Ottenberg and Fox have suggested that it is due to the presence of colored derivatives of sulfanilamide produced in the body. Mull and Smith suggested decreased oxygen saturation of the blood as its cause and advocated the administration of oxygen and measures for increasing the capacity of the blood for absorbing oxygen for its relief, but King and Leslie stated that observations on 8 patients tended to indicate that diminished oxygen saturation (increased unsaturation) of the arterial blood did not play any significant role in the cyanosis from sulfanilamide. It is evident, therefore, that its cause is still uncertain, but clinically it can be usually disregarded, and it disappears when administration of the drug is stopped and sometimes even when it is not.

6 *Fever*—Fever, which may be high, occasionally occurs, and usually the rise in temperature is noted seven to ten days after the beginning of treatment and hence may be mistaken for a recrudescence of the original infection, although in most instances there is no difficulty in reaching a decision, since the fever of infection is likely to have been normal or almost so for a few days before the sharp rise of drug fever sets in. In many respects the condition resembles serum sickness and for this reason has been considered due to allergy, but a more likely explanation is that it is a reaction to the products of lysed bacteria. Hageman and Blake noted its occurrence in 21 of 134 patients, and 9 of these also had a maculopapular erythema of wide distribution, but no evidence could be obtained of sensitization to sulfanilamide. Since drug fever, however, is frequently a warning of impending dermatitis, hemolytic anemia or neutropenia, treatment should be stopped when an unexplained fever develops. The question of safely resuming treatment, however, sometimes arises, and Long, Bliss and Feinstein advised under these conditions administration of 5 grains (0.32 Gm), if a sharp febrile response is noted within twelve hours it is unwise to continue giving the drug.

7 *Rashes*—Various rashes may occur, frequently preceded by drug fever and malaise. The eruption is usually maculopapular or morbilliform and brownish red, but sometimes it is purpuric. Usually

almost the entire body is affected, but in some instances the rash is limited to the buttocks or legs or is confined to the palms of the hands or soles of the feet, while the mucous membranes remain unaffected. There is usually no itching or discomfort. With discontinuance of treatment the eruption fades rapidly, and it may disappear anyhow in a few days even when treatment with sulfanilamide is continued. In ambulatory patients it is likely to occur on the exposed parts of the body and may be the result of photosensitization due to porphyrimia,⁶ which the drug is known to cause. The far more serious exfoliative dermatitis has occurred but is fortunately rare. Tedder, who has recently reviewed the literature and reported several cases, divided the patients with dermatitis into those whose condition was precipitated by exposure to sunlight, those definitely sensitive and with low tolerance and those with low tolerance and in whom dermatitis was due to saturation with sulfanilamide but without evidences of allergic sensitization.

8 *Anemia*—Hemolytic anemia associated with the administration of sulfanilamide was first described by Harvey and Janeway, whose publications were closely followed by case reports by Kohn and Willis. Since then a slowly developing mild anemia with slight reduction in erythrocytes and hemoglobin (10 to 20 per cent) has been commonly observed, especially when treatment is prolonged for ten days or longer. The condition is not accompanied by bilirubinemia, although urobilin is almost constantly present in the urine, and the reticulocytes may be slightly increased, as shown by Campbell, although the increase is not necessarily associated with anemia or leukopenia. Ordinarily it does not require a discontinuance of treatment, but whenever possible the hemoglobin should be estimated and the erythrocytes counted at daily intervals during the first week of heavy sulfanilamide treatment and once or twice a week thereafter, along with frequent examinations of the urine for urobilin as long as medication is continued.

Acute hemolytic anemia, however, has been reported by Wood in 24 per cent of a group of 378 adults and in 93 per cent of 144 children. It was characterized by rapid reduction in erythrocytes and hemoglobin, moderate to marked leukocytosis, marked reticulocytosis, bilirubinemia with jaundice, urobilinuria and, in certain instances, porphyrimuria, and was one of the most serious of the toxic manifestations of sulfanilamide therapy.

Within twenty-four to seventy-two hours after treatment is instituted the hemolytic anemia usually begins, with nausea, dizziness and fever, and appears to be the result of hypersensitiveness to the compound, without evidence that any one type of infection is a predisposing factor. When the condition is detected treatment should ordinarily stop, although the anemia may continue to progress in some instances and

6 Wien, Rimington and Hemmings

may recur if and when treatment is resumed. To the best of my knowledge no fatalities have been reported, as the condition readily yields to treatment with blood transfusions and, indeed, if a patient is critically ill, administration of sulfanilamide may be continued along with transfusions to maintain a proper level of erythrocytes and hemoglobin. As reported by Scott and Meerapfel, the prolonged administration of sulfanilamide and uleion (sulfanyldimethylsulfanilamide) may be followed by an alteration in the type of the blood serum, which precludes the finding of a suitable donor for blood transfusion.

9 *Leukopenia, Neutropenia and Agranulocytosis*—Mild transient leukopenia and neutropenia with monocytosis may occur in almost 40 to 50 per cent of patients on prolonged treatment with sulfanilamide.⁷ This complication usually occurs between the seventh and the twentieth day of treatment and is usually without relation to toxic symptoms but is significant when small doses are employed. It does not ordinarily require cessation of treatment, although when observed it indicates the advisability of daily or almost daily total and differential leukocyte counts for the detection of the more profound changes of agranulocytosis, which is the most dangerous of all the toxic manifestations, since the reported death rate is over 80 per cent. The cause of this profound depression of the bone marrow is unknown but is regarded as due to idiosyncrasy in the same way as with aminopyrine. To the best of my knowledge sulfapyridine is not more dangerous than sulfanilamide and neoprontosil, and agranulocytosis may occur with any of these compounds, especially in debilitated patients under prolonged therapy, since in most reported cases 35 Gm. or more had been taken in a period of two weeks or longer. Unfortunately, according to C. J. Young, examinations of the blood do not always forecast this sudden disaster, but fever or any toxic symptoms require caution in dosage for its prevention.

Among the earliest reports was that of Jennings and Southwell-Sander on 1 case, with the review of 4 others. Since then Johnston has reported 2 cases in which the agranulocytosis due to sulfanilamide and soluble prontosil was fatal and 1 case in which the condition due to sulfapyridine was fatal, and has given a review of 8 cases reported by others in which the conditions were caused by the former compounds. Schwartz, Garvin and Koletsky reported 1 death due to sulfanilamide, Berg and Holtzman, 1 death due to sulfanilamide, Coxon and Forbes and also Nicol and Freedman, 1 death due to sulfapyridine, and Corr and Root, 1 death after sulfanilamide. This does not cover all reported cases by any means, and there were deaths in the majority. Sutherland reported the recovery of a patient in whom the condition

7 Bigler, Clifton and Werner. Button and Howkins.

was caused by sulfapyridine. Dolgopol and Hobart have observed 2 patients with granulocytopenia (1 of whom died) and 2 patients with leukopenia apparently due to this compound and found that the damage to the bone marrow consisted in depression of the maturation of myeloid cells with occasional disturbance of erythropoiesis.

Apparently prolonged administration is far more dangerous than the giving of large doses over a short period of time, and fever has been the most constant premonitory sign. Of course, the administration of the compound should be promptly stopped and energetic treatment instituted, with repeated blood transfusions, pentnucleotide and liver extract. I have known, however, of 1 patient with agranulocytic angina with a severe hemolytic streptococcal infection to whom sulfanilamide was given in treatment and who made a prompt and satisfactory recovery, in spite of the agranulocytosis and sulfanilamide therapy.

10 *Miscellaneous Toxic Symptoms*—As previously stated, jaundice may occur in the course of severe hemolytic anemia, but toxic hepatitis is distinctly rare. Cases have been reported by Hageman and Blake and by Saphirstein, 2 cases by Bannick, Brown and Foster, in which the condition was fatal, and 5 cases by Garvin. In a number of these there was also exfoliative dermatitis. A case in which acute yellow atrophy of the liver following sulfanilamide medication was fatal has been reported by Cline.

Renal irritation is also distinctly rare, but Southworth and Cooke have recently reported 3 cases of hematuria associated with abdominal pain and nitrogen retention ascribed to the administration of sulfapyridine. Tsao and his colleagues have reported 5 cases of hematuria due to sulfapyridine in children, 1 of whom died, which they think may be associated with the formation of uroliths, especially since Gross, Cooper and Lewis have produced urinary calculi in 27 of 39 rats by the administration of this compound.

Toxic optic neuritis due to sulfanilamide has been reported by Bucy, 4 cases of peripheral neuritis ascribed to sulfanilylsulfanilamide compounds were reported by Wigton and Johnson, and 1 case of such a condition due to sulfanilamide was described by Ornsteen and Furst. As previously stated, peripheral neuritis has been especially reported in connection with the administration of the sulfanilylsulfanilamide compounds, and while the cause is unknown, most investigators have ascribed its occurrence to the toxic effects of lysed bacteria. Fisher and Gilmour have reported 2 cases in which encephalomyelitis followed the administration of sulfanilamide, with 1 death.

In conclusion, Jaubert and Motz have reported alleged impairment of spermatogenesis following the use of sulfanilamide in the treatment of gonorrhea in 30 per cent of patients, the condition was indicated

by low spermatozoa counts, verging on a state of azoospermia Harkness, however, as well as Heckel and Horri has not been able to confirm these findings, although Vigoni observed temporary impairment of motility in a proportion of 43 patients, which disappeared after an interval of a month in all but 1 Palazzoli and his colleagues failed to find any effect of sulfanilamide on spermatogenesis in rabbits, although Walker, Sigetti and Wiesner reported that the soluble prontosil may disorganize the germinal epithelium of mice without affecting the interstitial function with the dosage employed

In relation to the local applications of neoprontosil and sulfanilamide, it is interesting to note that Zaytzeff-Jern and Meleny found that these compounds, as well as sulfapyridine, are not destructive for bacteriophage and may be used with it in the treatment of mixed infections

BIBLIOGRAPHY

- Abramson, A W, and Flacks, B Staphylococcal Septicemia Complicating Carbuncle of the Face, *Lancet* **2** 1065, 1939
- Agar, F L, Hesseltine, H C, and Hac, L R Experimental Study of the Behavior of Sulfanilamide, *J A M A* **111** 766 (Aug 27) 1938
- Agranat, A L, Dreosoti, A A, and Ordman, D Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine (M & B 693), *Lancet* **1** 309, 1939
- Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine (M & B 693), *ibid* **1** 380, 1939
- Albright, F, Dienes, L and Sulkowitch, H W Pyelonephritis with Nephrocalcinosis, *J A M A* **110** 357 (June 4) 1938
- Allan, W B, Mayer, S, and Williams, R Pneumococcus Meningitis with Recovery, *Am J M Sc* **196** 99, 1938
- Allison, S T, and Myers, R Treatment of Pulmonary Tuberculosis with Sulfapyridine, *J A M A* **113** 1631 (Oct 28) 1939
- Alsted, G Type III Pneumococcal Pneumonia Effect of M & B 693, *Lancet* **1** 869, 1939
- Anderson, E D Hemolytic Streptococcus Meningitis Report of a Case with Recovery After the Use of Prontosil and Sulfanilamide, *J A M A* **108** 1591 (May 8) 1937
- Anderson, T, Cooper, E D, Cairns, J G, and Brown, D R Sulfapyridine in Treatment of Pneumococcus (Type II) Pneumonia, *Lancet* **2** 776, 1939
- Anderson, T F, and Dowdeswell, R M Treatment of Pneumonia with M & B 693, *Lancet* **1** 252, 1939
- Anwyl-Davies, T Sulphanilamide in the Treatment of Gonococcal Infections, *Brit M J* **2** 553, 1937
- Applebaum, E Sulfanilamide and Related Compounds in Treatment of Meningitis Secondary to Ear and Sinus Infections, *Laryngoscope* **48**.482, 1938
- Appleyard, J Personal communication to the author
- Archer, H E, and Discombe, G Sulphaemoglobinaemia Its Cause and Prevention, with Special Reference to Treatment with Sulphanilamide, *Lancet* **2** 432, 1937
- Arnold, J G Treatment of Hemolytic Streptococcal Meningitis with Para-Amino-Benzene Sulfonamide Report of a Case with Recovery, *Ann Int Med* **10** 1198, 1937

- Bar, F Chemotherapeutische Versuche bei der experimentellen Infektion der Maus mit Lymphogranuloma inguinale, *Klin Wchnschr* **17** 588, 1938
- Baker, J K Clostridium Welchii Septicemia and Peritonitis in the Puerperium Recovery After M & B 693 and Serum, *Lancet* **2** 646, 1939
- Ballou, H C, and Guernon, A The Effect of Sulfanilamide upon the Development of Experimental Tuberculosis in the Guinea Pig, *J Thoracic Surg* **8** 188, 1938
- Banks, H S Serum and Sulfanilamide in Acute Meningococcal Meningitis A Preliminary Survey Based on One Hundred and Thirteen Cases, *Lancet* **2** 7, 1938
- Primary Peritonitis in Scarlet Fever Treated with Sodium Salt of M & B 693, *ibid* **1** 983, 1939
- Chemotherapy of Meningococcal Meningitis, *ibid* **2** 921, 1939
- Bannick, E G, Brown, A E, and Foster, F P Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds Further Clinical Observations, *J A M A* **111** 770 (Aug 27) 1938
- Barbour, F A, and Towsley, H A Experience with Sulfanilamide in Treatment of Gonorrheal Ophthalmia, *Arch Ophth* **22** 581 (Oct) 1939
- Barer, H Typhoid Bacilluria Treated with Sulphanilamide, *Lancet* **2** 964, 1937
- Barker, R H Placental Transfer of Sulfanilamide, *New England J Med* **219** 42, 1938
- Barlow, O W, and Homburger, E Specific Chemotherapy of Experimental Staphylococcus Infections with Thiazol Derivatives, *Proc Soc Exper Biol & Med* **42** 792, 1939
- Barnett, H L, Hartman, A F, Perley, A M, and Ruhoff, M B Treatment of Pneumococcal Infections in Infants and Children with Sulfanilamide, *J A M A* **112** 518 (Feb 11) 1939
- Basman, J, and Perley, A M Report of Patients Treated with Sulfanilamide at the St Louis Children's Hospital, *J Pediat* **11** 212, 1937
- Batchelor, R C L, Lees, R, Murrell, M, and Braine, G I H 2-Sulphanilyl-Amidopyridine (M & B 693) in Treatment of Gonorrhea, *Brit M J* **2** 1142, 1938
- Becker, W Die Behandlung des Erysipels mit Prontosil, *Dermat Wchnschr* **104** 221, 1937
- Berg, S, and Holtzman, M Fatal Granulocytopenia Following Sulfanilamide Therapy, *J A M A* **110** 370 (Jan 29) 1938
- Bieter, R N, Larson, W P, Levine, M, and Cranston, E M Protective Action of Sulfapyridine Against Type II Pneumococcal Infections in Mice *Proc Soc Exper Biol & Med* **41** 202, 1939
- Bigler, J A, Clifton, W M, and Werner, M Leukocyte Response to Sulfanilamide Therapy, *J A M A* **110** 343 (Jan 29) 1938
- Bliss, E A, and Long, P H Comparative Therapeutic Effects of Sulfapyridine in Experimental Staphylococcus Aureus Infections in Mice, *Proc Soc Exper Biol & Med* **40** 32, 1939
- Feinstone, W H, Garrett, A W, and Long, P H Sulfapyridine and Sulfanilamide in Experimental Pneumococcal, Meningococcal, Welch Bacillary and Friedlander's Bacillary Infections in Mice, *ibid* **40** 619, 1939
- Long, P H, and Feinstone, W H The Differentiation of Streptococci and Its Relationship to Sulfanilamide Therapy, *South M J* **31** 303, 1938
- Bloch, H, and Pacella, B L Staphylococcal Meningitis Report of a Case in a Seventeen Day Old Infant Successfully Treated with Sulfanilamide, *J A M A* **110** 508 (Feb 12) 1938

- Bohlman, H R Gas Gangrene Treated with Sulfanilamide Report of Three Cases, J A M A **109** 254 (July 24) 1937
- Bowie, F J T , Anderson, T E , Dawson, A , and Mackay, J F Treatment of Gonorrhea by M & B 693, Brit M J **1** 711, 1939
- Branham, S E The Effect of Sulfapyridine and Sulfanilamide With and Without Serum in Experimental Meningococcus Infection, Pub Health Rep **55** 12, 1940
- and Rosenthal, S M Studies in Chemotherapy Sulphanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infection in Mice, *ibid* **52** 685, 1937
- Bricker, E M , and Graham, E A The Inhibitory Effect of Sulfanilamide on Wound Healing, J A M A **112** 2593 (June 24) 1939
- Britton, C J C , and Howkins, J Action of Sulphanilamide on Leucocytes A Report on Fifty Ambulant Patients, Lancet **2** 718, 1938
- Brown, A E , Herrell, W E , and Bargaen, J A Neoprontosil (Oral) in Treatment of Chronic Ulcerative Colitis, Proc Staff Meet , Mayo Clin **13** 561, 1938
- Brown, H W Ineffectiveness of Sulfanilamide in the Treatment of Canine Filariasis, Proc Soc Exper Biol & Med **39** 98, 1938
- Brown, J L Prontosil by Intrapleural Route Two Cases of Streptococcal Empyema, Brit M J **1** 1157, 1937
- Brown, T M Protective Action of Sulfanilamide and Antimeningococcus Serum on Meningococcus Infection of Mice, Bull Johns Hopkins Hosp **61** 272, 1937
- Brule, M , Hillemand, P , and Vilde, L Deux cas de rhumatisme gonococcique traités par la para-amino-phényl-sulfamide, Bull et mem Soc med d hop de Paris **53** 1650, 1937
- Bryant, J , and Fairman, H D Chemotherapy of Cerebrospinal Fever in the Field, Lancet **1** 923, 1939
- Bucy, P C Toxic Neuritis Resulting from Sulfanilamide, J A M A **109** 1007 (Sept 25) 1937
- Buttle, G A H Discussion on the Treatment of Bacterial Diseases with Substances Related to Sulphanilamide, Proc Roy Soc Med **31** 154, 1937
- Gray, W R , and Stephenson, D Protection of Mice Against Streptococcal and Other Infections by p-Aminobenzenesulphonamide and Related Substances, Lancet **2** 1286, 1936
- and Parish, H J Treatment of Tuberculosis in Guinea Pigs with Sulphanilamide, Brit M J **2** 776, 1938
- Parish, H J , McLeod, M , and Stephenson, D The Chemotherapy of Typhoid and Some Other Non-Streptococcal Infections in Mice, Lancet **1** 681, 1937
- The Treatment of Streptococcal Infections in Mice with 4 4' Diaminodiphenylsulphone, *ibid* **1** 1331, 1937
- Bynum, W T Recurrences of Undulant Fever (Brucellosis) Following the Administration of Sulfanilamide, J A M A **112** 835 (March 4) 1939
- Cable, J V Pneumococcal Meningitis A Review of Thirty-Nine Fatal Cases and a Report of Recovery After Administration of M & B Soluble, Lancet **2** 73, 1939
- Campbell, A D A Note on the Failure of Sulfanilamide to Affect Syphilis in the Rabbit, Am J Syph , Gonor & Ven Dis **21** 524, 1937
- Campbell, C M Effect of Sulphanilamide on the Blood Picture, Lancet **1** 247, 1938

- Campbell, D, and Morgan, T N Cyanosis Caused by Sulphonamide Compounds, *Lancet* **2** 123, 1939
- Carey, B W, Jr The Use of Para-Amino-Benzene-Sulfonamide and Its Derivatives in the Treatment of Infections Due to Beta Streptococcus Hemolyticus, the Meningococcus and Gonococcus, *J Pediat* **11** 202, 1937
- Caro, M R Pemphigus Treated with Sulfanilamide Preliminary Report, *Arch Dermat & Syph* **37** 196 (Feb) 1938
- Carpenter, C M, and Baibou, G M Effect of Neoprontosil on Bacterial Toxins, *Proc Soc Exper Biol & Med* **41** 255, 1939
- Cawthorne, T Streptococcal Meningitis Sulfanilamide in Its Management, *Lancet* **1** 304, 1938
- Chandler, C A, and Janeway, C A Observations on the Mode of Action of Sulfanilamide in Vitro, *Proc Soc Exper Biol & Med* **40** 179, 1939
- Chinn, B D In Vitro and In Vivo Effect of Sulfanilamide on *Brucella abortus* and *Brucella suis*, *Proc Soc Exper Biol & Med* **38** 732, 1938
- The Use of Sulfanilamide in Experimental Brucellosis, *J Infect Dis* **64** 78, 1939
- Clark, A L Sulfanilamide in Treatment of Nonspecific Infections of the Urinary Tract, *J A M A* **112** 719 (Feb 25) 1939
- Climenko, D R, Crossley, M L, and Northey, E H Protective Action of Certain Sulfanilamide Derivatives in Experimental Influenza Infections, *J A M A* **110** 2099 (June 18) 1938
- Cline, E W Acute Yellow Atrophy of the Liver Following Sulfanilamide Medication, *J A M A* **111** 2384 (Dec 14) 1938
- Coburn, A F, and Moore, L V Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections with Special Reference to Rheumatic Fever, *J Clin Investigation* **18** 147, 1939
- Coggeshall, L T Prophylactic and Therapeutic Effect of Sulfonamide Compounds in Experimental Malaria, *Proc Soc Exper Biol & Med* **38** 768, 1938
- The Selective Action of Sulfanilamide on the Parasites of Experimental Malaria in Monkeys and in Vivo and in Vitro, *J Exper Med* **71** 13, 1940
- Cohn, A The Effect of Sulfanilamide on Gonococci, *Am J Syph, Gonorr & Ven Dis* **22** 1, 1938
- and Peizer, L R Further Studies of the Experimental Gonococcal Infection in Mice and Their Protection by Sulfanilamide, *J Infect Dis* **63** 77, 1938
- Cokkims, A J, and McElligott, G L M Sulphanilamide in Gonorrhoea An Analysis of Six Hundred and Thirty-Three Cases, *Lancet* **2** 355, 1938
- Colebrook, L, and Kenny, M Treatment of Human Puerperal Infections, and of Experimental Infections in Mice, with Prontosil, *Lancet* **1** 1279, 1936
- Treatment with Prontosil of Puerperal Infections Due to Hemolytic Streptococci, *ibid* **2** 1319, 1936
- Prophylactic Treatment in Obstetrics by Means of Prontosil and Sulfanilamide, *ibid* **2** 286, 1937
- The Treatment of One Hundred and Six Cases of Puerperal Fever by Sulfanilamide (Streptocide), *ibid* **2** 1237 and 1291, 1937
- Collins, E N Use of Sulfanilamide in Treatment of Chronic Ulcerative Colitis Preliminary Report of Eleven Cases, *Cleveland Clin Quart* **5** 161, 1938
- Cooper, F B, Gross, P, and Lewis, M Chemotherapy of Types VII and III Pneumococcal Infections with Sulphanilamide, 4,4'-Di-(Acetylamino)-Diphenylsulphone and 4,4'-Diamino-Benzenesulphonamide, *Am J M Sc* **196** 343, 1938
- Sulfone and Sulfonamide Therapy in Streptococcal Infections, *Proc Soc Exper Biol & Med* **38** 375, 1938

- Chemotherapy of B Pertussis Infections of Mice, *ibid* **38** 407, 1938
- Chemotherapy of Pneumococcal (Type II) Meningitis in the Rat, *ibid* **38** 835, 1938
- Sulfonamide Therapy of Experimental Peritonitis Due to B Coli, B Proteus and B Pyocyaneus, *ibid* **40** 34, 1939
- Chemotherapy of Experimental Rabies in Rats, *ibid* **40** 649, 1939
- Gross, P, and Mellon, R R Action of p-Aminobenzenesulfonamide on Type III Pneumococcus Infections in Mice, *ibid* **36** 148, 1937
- Efficacy of p-Aminobenzenesulfonamide in Experimental Type III Pneumococcus Pneumonia of Rats, *ibid* **36** 225, 1937
- P-Aminobenzenesulfonamide and Antipneumococcal Serum Therapy in Type I Pneumococcal Infections of Rats, *ibid* **36** 535, 1937
- Para-Aminobenzenesulfonamide Therapy in Experimental Type III Pneumococcal Pneumonia, *ibid* **36** 678, 1937
- Chemotherapeutic Evaluation of Sulfanilamide and 2-(Sulfamido)-Pyridine in Type II Pneumococcal Infections in Mice and Rats, *ibid* **40** 37, 1939
- Corr, P, and Root, R N Death from Granulocytopenia After Sulfanilamide Therapy, *J A M A* **112** 1939 (May 13) 1939
- Coxon, R V, and Forbes, J R Agranulocytic Angina Following Administration of M & B 693, *Lancet* **2** 1412, 1938
- Crean, T F The Use of Prontosil in the Treatment of Gonorrhea, *Lancet* **2** 895, 1937
- Cruickshank, J C Chemotherapy of Experimental Anthrax Infection, *Lancet* **2** 681, 1939
- Cunningham, A A Pneumococcal Meningitis Treated with Sulphanilamide and M & B 693, *Lancet* **2** 1114, 1938
- Curtis, W L Sulfanilamide in the Treatment of Tularemia, *J A M A* **113** 294 (July 22) 1939
- Custer, R P, Forster, H W, Lamotte, W A, Patton, D M, and Phinney, J A Changes in the Central Nervous System in Sulfanilamide Intoxication, *Arch Path* **26** 904 (Oct) 1938
- Cuthbert, J C The Treatment of Urinary Infections in the Puerperium, *Lancet* **2** 720, 1938
- Cutts, M, Gregory, K K, and West, E J Pneumococcal Meningitis Successfully Treated with Sulfanilamide, *J A M A* **112** 1456 (April 15) 1939
- Dalrymple-Champneys, W Control of Common Fevers Undulant Fever, *Lancet* **2** 326, 1938
- Davis, H A, Harris, L C, Jr, and Schmeisser, H C Tissue Changes Following Prolonged Administration of Sulfanilamide in Rats, *Arch Path* **25** 750 (May) 1938
- Dees, J E, and Colston, J A C The Use of Sulfanilamide in Gonococcal Infections, *J A M A* **108** 1855 (May 29) 1937
- Diaz de Leon, A Treatment of Malaria with Sulfonamide Compounds, *Pub Health Rep* **52** 1460, 1937
- Dickerson, V C, and Whitney, L F Sulfanilamide and Prontosil in the Treatment of Canine Distemper, *Proc Soc Exper Biol & Med* **38** 263, 1938
- Diefenbach, W E, and Yuskis, A S Typhoid Septicemia Treated with Sulfanilamide, *California & West Med* **49** 146, 1938
- Dietrich, H F Prontosil in Experimental Tuberculosis Preliminary Report, *Am Rev Tuberc* **38** 389, 1938

- Dimson, S B Chronic Meningococcal Septicaemia Treated with 2-(p-Aminobenzenesulphamido) Pyridine, *Lancet* **2** 424, 1938
- Dochez, A R, and Slanetz, C A Treatment of Canine Distemper with Chemotherapeutic Agent, Sodium Sulfanilyl Sulfamate, *Science* **87** 43, 1938
- Dolgopoi, V B, and Hobart, H M Granulocytopenia in Sulfapyridine Therapy, *J A M A* **113** 1012 (Sept 9) 1939
- Domagk, G Chemotherapy of Bacterial Infections, *Angewandte Chem* **48** 657, 1935
- Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsche med Wchnschr* **61** 250, 1935
- Chemotherapie der Streptokokkeninfektionen, *Klin Wchnschr* **15** 1585, 1936
- Untersuchungen über den Wirkungsmechanismus des Prontosil bei der experimentellen Streptokokkeninfektion, *Ztschr f klin Med* **132** 775, 1937
- Weitere Untersuchungen über die chemotherapeutische Wirkung Sulfonamidhaltiger Verbindungen bei bakteriellen Infektionen, *Klin Wchnschr* **16** 1412, 1937
- Dowling, H F, and Abernethy, T J The Treatment of Pneumococcus Pneumonia A Comparison of the Results Obtained with Specific Serum and with Sulfapyridine, *Am J M Sc* **199** 55, 1940
- Earle, K V Lymphopathia Venereum Treated with M & B 693, *Lancet* **1** 985, 1939
- M & B 693 in Lymphopathia Venereum, *ibid* **2** 1265, 1939
- Eldahl, A Intrathecal Sulphanilamide in Meningococcal Meningitis, *Lancet* **1** 712, 1938
- Eley, R C, in discussion on Neal
- Ellis, G R Treatment of Subacute Bacterial Endocarditis with M & B 693, *Lancet* **2** 1521, 1938
- Erskine, D, and Royds, J E Agranulocytosis Complicating Treatment of Acute Pemphigus with M & B 693, *Lancet* **2** 1366, 1939
- Evans, G M, and Gailsford, W F Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine, *Lancet* **2** 14, 1938
- Fagerstrom, D P Sulfanilamide Therapy in Erosive and Gangrenous Balanitis, *Urol & Cutan Rev* **41** 858, 1937
- Faget, G H, Palmer, M R, and Sherwood, R O Unsuccessful Treatment of Malaria with Sulfonamide Compounds, *Pub Health Rep* **53** 1364, 1938
- Feinstone, W H, Bliss, E A, Ott, E, and Long, P H Observations Concerning Toxicity, Absorption and Therapeutic Effect of Sulphanilamide and Certain Related Organic Sulphur-Containing Compounds in Experimental Infections in Mice, *Bull Johns Hopkins Hosp* **62** 565, 1938
- Feldman, W H, and Hinshaw, H C Effect of Sulfapyridine on Experimental Tuberculosis in the Guinea Pig, *Proc Staff Meet, Mayo Clin* **14** 174, 1939
- Felke, H Wie soll sich der Arzt in der Praxis zur Chemotherapie der Gonorrhoe stellen? *Munchen med Wchnschr* **84** 1867, 1937
- Fenton, W J, and Hodgkiss, F Staphylococcal Septicaemia Treated with M & B 693, *Lancet* **2** 667, 1938
- Ferguson, C, Buckholtz, M, and Gromet, R Y Sulphanilamide Therapy in Gonorrhea Review of Literature and Report of Two Hundred and Ninety-Eight Cases, *Am J M Sc* **197** 452, 1939
- Fernandez, L J, and Fernandez, R F Sulfanilamide in Gonorrheal Ophthalmia Preliminary Report, *Am J Ophth* **21** 763, 1938
- Fickling, B W, Pincus, P, and Boyd-Cooper, B M & B 693 in the Saliva, *Lancet* **2** 1310, 1939

- Finland, M, and Brown, J W Specific Treatment of Type I Pneumonia Including the Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, *Am J M Sc* **197** 151, 1939
- Specific Treatment of Pneumococcus Type II Pneumonia Including the Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, *ibid* **197** 369, 1939
- Specific Treatment of Pneumococcus Type V and Type VII Pneumonias Including the Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, *ibid* **197** 381, 1939
- Specific Serotherapy and Chemotherapy of the Pneumococcus Pneumonias, *Ann Int Med* **12** 1816, 1939
- Brown, J W, and Raugh, A E Treatment of Pneumococcic Meningitis Study of Ten Cases Treated with Sulfanilamide Alone or in Various Combinations with Specific Antipneumococcic Serum and Complement, *New England J Med* **218** 1033, 1938
- Fisher, J H, and Gilmour, J R Encephalomyelitis Following Administration of Sulphanilamide, *Lancet* **2** 301, 1939
- Flippin, H F, and Pepper, D S The Use of 2-(p-Aminobenzenesulphonamide) Pyridine in the Treatment of Pneumonia, *Am J M Sc* **196** 509, 1938
- The Treatment of Pneumococcic Pneumonia with Sulfapyridine A Progress Report on Observations on One Hundred Cases, *J A M A* **112**.529 (Feb 11) 1939
- Foerster Sepsis im Anschluss an ausgedehnte Peritonitis Heilung durch Streptozon, *Zentralbl f Haut- u Geschlechtskr* **45** 549, 1933
- Fosbinder, R J, and Walter, L A Sulfanilamide Derivatives of Heterocyclic Amines, *J Am Chem Soc* **61** 2032, 1939
- Foulis, M A, and Bari, J B Prontosil Album in Puerperal Sepsis, *Brit M J* **1** 445, 1937
- Francis, A E Sulphanilamide in the Treatment of Undulant Fever, *Lancet* **1** 496, 1938
- Fuhs, H, and Volavsek, W Zur Chemotherapie der Gonorrhoe, *Wien klin Wchnschr* **51** 586, 1938
- Ergänzende Bemerkungen zur Chemotherapie der Gonorrhoe, *Dermat Wchnschr* **107** 1057, 1938
- Gailsford, W F, Evans, G M, and Whitelaw, W Parenteral Therapy with M & B 693 Soluble, *Lancet* **2** 69, 1939
- Galewski, S, and Stannus, H S Septicemia Due to Staphylococcus Albus Treated with M & B 693, *Lancet* **2** 1067, 1939
- Garvin, C F Toxic Hepatitis Due to Sulfanilamide, *J A M A* **111** 2283 (Dec 17) 1938
- Gaudin, H J, Zide, H A, and Thompson, G J Use of Sulfanilamide After Transurethral Prostatectomy, *J A M A* **110** 1887 (June 4) 1938
- Gay, F P, and Clark, A R On the Mode of Action of Sulfanilamide in Experimental Streptococcus Empyema, *J Exper Med* **66** 535, 1937
- The Mode of Action of Sulfanilamide on Streptococcus, *ibid* **69** 607, 1939
- Gelmo, P Sulphamides of p-Aminobenzenesulphonic Acid, *J prakt Chem* **77** 369, 1908
- Gennerich, W, and Gennerich, K Ulron bei der Gonorrhoebehandlung, *Dermat Wchnschr* **106** 541, 1938
- Gley, P, and Girard, A Un nouveau dérive de la sulfamido-chrysordine très actif contre l'infection streptococcique, *Presse med* **44** 1775, 1936
- Greenblatt, R B, and Sanderson, E S Sulfanilamide in Chancroid Disease, *Am J Syph, Gonorr & Ven Dis* **23** 605, 1939

- Greey, P H , Campbell, H H , and Culley, A W Effect of Sulfanilamide on Experimental Tuberculosis in the Guinea Pig, *Proc Soc Exper Biol & Med* **39** 22, 1938
- Sulphanilamide and Related Compounds in Experimental Tuberculosis, *ibid* **40** 418, 1939
- Gregg, L A , Looshi, C G , and Hamburger, M Sulfapyridine in Experimental Lobar Pneumonia in the Dog, *Proc Soc Exper Biol & Med* **41** 459, 1939
- Gross, P , Cooper, F B , and Lewis, M The Chemotherapy of Experimental Type II Pneumococcic Meningitis, *Am J M Sc* **197** 609, 1939
- Urinary Calculi Caused by Sulfapyridine, *Urol & Cutan Rev* **43** 299, 1939
- Grutz, O Neue Grundlegung für die Gonorrhoebehandlung, *Munchen med Wchnsch* **84** 1201, 1937
- Hageman, P O Toxicity of Sulfanilamide A Study of the Pathological Lesions in White Mice, *Proc Soc Exper Biol & Med* **37** 119, 1937
- and Blake, F G Specific Febrile Reaction to Sulfanilamide Drug Fever, *J A M A* **109** 642 (Aug 28) 1937
- Clinical Experience with Sulphanilamide in the Treatment of Beta Hemolytic Streptococcic Infections, *Am J M Sc* **195** 163, 1938
- Hall, W E B Sulphanilamides in Tertian Malaria, *J Pharmacol & Exper Therap* **63** 353, 1938
- Hamilton, T R , and Neff, F C Influenzal Meningitis with Bacteremia Treated with Sulfapyridine Recovery, *J A M A* **113** 1123 (Sept 16) 1939
- Hanschell, H M Sulfanilamide in the Treatment of Chancroid, *Lancet* **1** 887, 1938
- Harkelroad, F S Sulfanilamide in the Treatment of Typhoid Fever, *West Virginia M J* **34** 549, 1938
- Harkness, A H Sulphanilamide and Spermatozoa, *Lancet* **2** 1490, 1938
- Harley, R D , Brown, A E , and Herrell, W E Sulfanilamide and Neoprontosil in the Treatment of Trachoma, *Proc Staff Meet, Mayo Clin* **14** 641, 1939
- Harries, E H R , Swyer, R , and Thompson, N Sulfanilamide in Typhoid Fever, *Lancet* **1** 1321, 1939
- Harris, J S , and Klein, J R Acetylation of Sulfanilamide by Liver Tissue in Vitro, *Proc Soc Exper Biol & Med* **38** 78, 1938
- Haitmann, A F , Peirley, A M , and Barnett, H L Study of Some of the Physiological Effects of Sulfanilamide Changes in Acid Base Balance, *J Clin Investigation* **17** 465, 1938
- Methemoglobin Formation and Its Control, *ibid* **17** 699, 1938
- Harvey, A M , and Janeway, C A Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide (Para-Aminobenzenesulfonamide), *J A M A* **109** 12 (July 3) 1937
- Hauschild, F Untersuchungen über die Wirkung einiger Redoxyfarbstoffe bei Zuständen gestörter Atmung Katalysin (Thionin) und Methamoglobin Vergiftung, *Arch f exper Path u Pharmacol* **182** 118, 1936
- Havens, W P , Hansen, L P , and Kramer, C G Effect of Sulfapyridine in Pneumococcus Type I Infections in Rabbits, *Proc Soc Exper Biol & Med* **42** 408, 1939
- Hawking, F Pharmacological Actions of Sulfanilamide, *Lancet* **2** 1019, 1937
- Hebb, A , Sullivan, S G , and Felton, L D The Treatment of Lymphopathia Venereum with Sodium Sulfamylol Sulfanilate and Sodium Sulfanilate, *Pub Health Rep* **54** 1750, 1939

- Heckel, N J , and Hori, C G The Effect of Sulfanilamide upon Spermatogenesis in Man, *Am J M Sc* **198** 347, 1939
- Helmholtz, H F Urinary Infections in Infancy and Childhood Diagnosis and Treatment, *J A M A* **111** 1719 (Nov 5) 1938
- Herrold, R D Treatment of Gonorrhea and Other Infections in Urinary Tract with Sulfanilamide, *Urol & Cutan Rev* **41** 468, 1937
- Hewell, B A , and Mitchell, A G The Treatment of Pneumococcic Meningitis with Sulfanilamide, *J A M A* **112** 1033 (March 18) 1939
- Hill, R A , and Goodwin, M H "Prontosil" In Treatment of Malaria Report of One Hundred Cases, *South M J* **30** 1170, 1937
- Hoare, E D Case for Prophylaxis with Sulphanilamide and M & B 693, *Lancet* **1** 76, 1939
- Hobson, F G , and MacQuaide, D H G Treatment of Meningococcal Meningitis with 2-Sulphanilyl-Amidopyridine (M & B 693), *Lancet* **2** 1213, 1938
- Hodes, H L , Gimbel, H S , and Burnett, G W Treatment of Pneumococcic Meningitis with Sulfapyridine and the Sodium Salt of Sulfapyridine, *J A M A* **113** 1614 (Oct 28) 1939
- Horlein, H The Chemotherapy of Infectious Diseases Caused by Protozoa and Bacteria, *Proc Roy Soc Med* **29** 313, 1935
- Hoffman, S J , Schneider, M , Blatt, M L , and Herrold, R D Sulfanilamide in the Treatment of Gonorrheal Vulvovaginitis, *J A M A* **110** 1541 (May 7) 1938
- Hutchison, A Treatment of Bubo with Sulfanilamide, *Lancet* **1** 1047, 1938
- Ingels, A E Lupus Erythematosus Treated with Sulfanilamide, *Arch Dermat & Syph* **37** 879 (May) 1938
- Jaeger, K H Ueber ortliche Prontosilanwendung, *Deutsche med Wchnsch* **62** 1831, 1936
- Jaubert, A , and Motz, C Action inhibitrice de certains dérivés organiques du soufre sui la spermatogénese de l'homme, *Bull Soc franç d'urol*, 1938, p 60
- Jennings, G H , and Southwell-Sander, G Anaemia and Agranulocytosis During Sulphanilamide Therapy, *Lancet* **2** 898, 1937
- Jewesbury, E C O The Use of Sulphanilamide in the Treatment of Meningococcal Meningitis, *Lancet* **1** 1262, 1938
- Johnson, S H , Leberman, P R , Pepper, D S , and Lynch, H The Use of Sulfapyridine in the Treatment of Gonococcal Urethritis in the Male, *Am J M Sc* **198** 594, 1939
- Johnston, F D Granulocytopenia Following the Administration of Sulphanilamide Compounds, *Lancet* **2** 1044, 1938
- Agranulocytosis Following Treatment with M & B 693, *ibid* **2** 1200, 1938
- Keefer, C S Subacute Bacterial Endocarditis Active Cases Without Bacteremia, *Ann Int Med* **11** 714, 1937
- and Rantz, L A Sulfanilamide A Study of Its Effect on the Bactericidal Power of Whole Blood for the Gonococcus, *Am J Syph, Gonor & Ven Dis* **22** 679, 1938
- Sulphanilamide in the Treatment of Gonococcal Arthritis, *Am J M Sc* **197** 168, 1939
- Sulfanilamide A Study of Its Mode of Action on Hemolytic Streptococci, *Arch Int Med* **63** 957 (May) 1939
- Kelson, S R Use of Sulphanilamide (Para Amino Benzene Sulphonamide) in Experimental Poliomyelitis, *Proc Soc Exper Biol & Med* **36** 718, 1937
- and White, P D Treatment of Subacute Bacterial Endocarditis, *J A M A* **113** 1700 (Nov 4) 1939

- Kenny, M , Johnston, F D , von Haebler, T , and Miles, A A *p*-Aminobenzene-sulphonamide in Treatment of Bacterium Coli Infections of the Urinary Tract, *Lancet* **2** 119, 1937
- Kepl, M , and Gunn, F D Sulfapyridine and Serum Therapy in Experimental Lobar Pneumonia of Rats, *Proc Soc Exper Biol & Med* **40** 529, 1939
- Sulfanilamide and Sulfapyridine in Type III Lobar Pneumonia of Rats, *ibid* **41** 457, 1939
- King, F H , and Leslie, A Oxygen Saturation of Arterial Blood in Cyanosis from Sulfanilamide, *J A M A* **110** 2069 (June 18) 1938
- King, J T , Henschell, A F , and Green, B S The Bacteriostatic and Antitoxic Actions of Sulfanilamide Tissue Culture Studies, *J A M A* **113** 1704 (Nov 4) 1939
- Kirk, R , McKelvie, A R , and Russe, H A Sulfanilamide in the Treatment of Trachoma, *Lancet* **2** 994, 1938
- Klee, P , and Romer, H Prontosil bei Streptokokkenkrankungen, *Deutsche med Wchnschr* **61** 253, 1935
- Knight, A A , and David, V C Treatment of Venereal Lymphogranuloma with Sulfanilamide, *J A M A* **112** 527 (Feb 11) 1939
- Kohn, S E Acute Hemolytic Anemia During Treatment with Sulfanilamide, *J A M A* **109** 1005 (Sept 25) 1937
- Kolmer, J A Principles and Practice of Chemotherapy with Special Reference to the Treatment of Syphilis, Philadelphia, W B Saunders Company, 1926, p 62
- Brown, H , and Raiziss, G W Chemotherapy of Experimental Streptococcus Infections of Rabbits with Special Reference to Pyridine Compounds and Prontosil Soluble, *J Pharmacol & Exper Therap* **61** 253, 1937
- Raiziss, G W , and Rule, A M Sulfanilamide and Derivatives in the Treatment of Experimental Tuberculosis of Guinea Pigs, *Proc Soc Exper Biol & Med* **39** 581, 1938
- Sulfanilamide and Diaminodiphenylsulfone and Their Diacetyl Derivatives in the Treatment of Experimental Intradermal Streptococcus Infections of Rabbits, *ibid* **39** 95, 1938
- Toxicity, Therapeutic Activity, and Mode of Action of Sulfanilamide in Experimental Streptococcus Infections of Rabbits, *J Lab & Clin Med* **24** 164, 1938
- Sulfanilamide and Derivatives in the Treatment of Experimental Pneumococcus Infections, *ibid* **24** 779, 1939
- and Rule, A M Experimental Streptococcus Infections in Rabbits for Therapeutic Investigations, *ibid* **22** 1097, 1937
- Sulfanilamide and Sulfapyridine in Treatment of Experimental B Friedlander (Klebsiella Pneumoniae) Infections of Mice, *Proc Soc Exper Biol & Med* **42** 305, 1939
- Sulfanilamide and Sulfapyridine in Treatment of Experimental B Typhosus (Eberthella Typhosus) Infections of Mice, *ibid* **40** 615, 1939
- Sulfanilamide and Sulfapyridine in Treatment of Experimental B Coli (Escherichia coli) Infections of Mice, *ibid* **42** 307, 1939
- Sulfanilamide in the Treatment of Experimental Trypanosomiasis of Rats, *ibid* **40** 77, 1939
- The Therapeutic Activity of Sulfanilamide and Allied Compounds in Experimental Brucellosis of Mice, *J Pharmacol & Exper Therap* **68** 406, 1940
- Rule, A M , and Werner, M L Sulfanilamide in the Treatment of Experimental Streptococcal and Pneumococcal Meningitis, *Arch Otolaryng* **27** 519 (May) 1938

- Kornblith, B A , Jacoby, A , and Wishengrad, M Treatment of Chancroid with Sulfanilamide, *J A M A* **111** 523 (Aug 6) 1938
- Sulfanilamide in Treatment of Chancroid, *New York State J Med* **39** 364 1939
- Kracke, R R Relation of Drug Therapy to Neutropenic States, *J A M A* **111** 1255 (Oct 1) 1938
- Kreidler, W A Treatment of Pneumococcal Infections in Rabbits with Sulfanilamide, *Proc Soc Exper Biol & Med* **37** 146, 1937
- Ladd, W E , Botsford, T W , and Curnen, E C Primary Peritonitis in Infants and Children A More Effective Treatment, *J A M A* **113** 1455 (Oct 14) 1939
- Larimer, R N , and Wiesser, E G Human Equine Encephalomyelitis, *J Iowa M Soc* **29** 286, 1939
- Larson, W P , Bieter, R N , and Levine, M Protective Action of Sulfapyridine in Rabbits Infected with Pneumococci, *Proc Soc Exper Biol & Med* **40** 703, 1939
- Latto, C Pneumococcal Meningitis Treated with Piontosil, *Brit M J* **1** 566, 1938
- Lee, H M , Anderson, R C , and Chen, K K Passage of Sulfanilamide from Mother to Fetus, *Proc Soc Exper Biol & Med* **38** 366, 1938
- Levaditi, C Chimiotherapie de la lymphogranulomatose inguinale experimentale, *Compt rend Soc de biol* **128** 138, 1938
- and Vaisman, A La toxo-infection gonococcique experimentale et son traitement chimiotherapique, *Presse med* **45** 1371, 1937
- Action curative et preventive du chlorhydrate de 4'-sulfamido-2,4-diamino-azobenzene dans la streptococcie experimentale, *Compt rend Soc de biol* **119** 946, 1935, **120** 1077, 1935, **121** 803, 1936
- Chimiotherapie de l'infection meningococcique experimentale de la souris, *ibid* **125** 604, 1937
- Lich, R , and Rowntree, G R Sulfanilamide Therapy in Acute Neisserian Urethritis, *Am J Syph, Gonorr & Ven Dis* **23** 323, 1939
- Lloyd, V E Recent Advances in Treatment of Gonorrhea, *Guy's Hosp Gaz* **52** 505, 1938
- Erskine, D , and Johnson, A G Chemotherapy of Gonorrhea with M & B 693, *Lancet* **2** 1160, 1938
- and others Discussion on Sulphonamide Therapy in Gonorrhea, *Brit J Ven Dis* **15** 100, 1939
- Lockwood, J S , Coburn, A F , and Stokinger, H E Studies on the Mechanism of Action of Sulfanilamide I The Bearing on the Character of the Lesion on the Effectiveness of the Drug, *J A M A* **111** 2259 (Dec 17) 1938
- Studies on the Mechanism of Action of Sulfanilamide The Effect of Sulfanilamide in Serum and Blood on Hemolytic Streptococci in Vitro, *J Immunol* **35** 155, 1938
- Loe, F Sulfanilamide Treatment of Trachoma Preliminary Report, *J A M A* **111** 1371 (Oct 8) 1938
- Loewenthal, H Combined Serum and Sulfanilamide in the Treatment of Streptococcal Infections in Mice, *Lancet* **1** 197, 1939
- Long, P H , and Bliss, E A Observations upon Experimental and Clinical Use of Sulfanilamide in Treatment of Certain Infections, *Canad M A J* **37** 457, 1937
- Para-Amino-Benzene-Sulfonamide and Its Derivatives Experimental and Clinical Observations on Their Use in the Treatment of Beta Hemolytic Streptococcal Infection, a Preliminary Report *J A M A* **108** 32 (Jan 2) 1937

- The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939
- Bliss, E A, and Feinstone, W H Mode of Action, Clinical Use and Toxic Manifestations of Sulfanilamide, *J A M A* **112** 115 (Jan 14) 1939
- Love, J W Nonhemolytic Streptococcal Meningitis Report of a Case Successfully Treated with Sulfanilamide and Prontosil, *J Lab & Clin Med* **23** 482, 1938
- McAlpine, D, and Thomas, G C Pneumococcal Meningitis Treated with M & B 693, *Lancet* **1** 754, 1939
- MacCallum, F A, and Findlay, G M Chemotherapeutic Experiments on the Virus of Lymphogranuloma Inguinale in the Mouse, *Lancet* **2** 136, 1938
- McCammon, W O Sulfanilamide in the Treatment of Smallpox, *J A M A* **112** 1936 (May 13) 1939
- McCoy, O R Ineffectiveness of Sulfanilamide in the Treatment of Trichiniasis of Rats, *Proc Soc Exper Biol & Med* **38** 461, 1938
- McGregor-Robertson, J G Acute Gonorrhoea Treated with M & B 693, *Lancet* **2** 1463, 1938
- McIntosh, J, and Whitby, L E H The Mode of Action of Drugs of the Sulphonamide Group, *Lancet* **1** 431, 1939
- McKee, C M, Rake, G, Greep, R O, and Van Dyke, H B Therapeutic Effect of Sulfathiazole and Sulfapyridine, *Proc Soc Exper Biol & Med* **42**, 417, 1939
- MacKeith, R C, and Oppenheimer, G Pneumococcal Meningitis Report of Five Consecutive Cases Treated with Sulfanilamide-Pyridine (M & B 693), *Lancet* **1** 1099, 1939
- McKinley, E B, Meck, J S, and Acree, E G Sulphanilamide and Virus Diseases, *Science* **87** 43, 1938
- MacLean, I H, Rogers, K B, and Fleming, A M & B 693 and Pneumococci, *Lancet* **1** 562, 1939
- MacLeod, C M Chemotherapy of Pneumococcal Pneumonia, *J A M A* **113** 1405 (Oct 7) 1939
- and Daddi, G A "Sulfapyridine-Fast" Strain of Pneumococcus Type I, *Proc Soc Exper Biol & Med* **41** 69, 1939
- Metabolism of "Sulfapyridine-Fast" and Parent Strains of Pneumococcus Type I, *ibid* **41** 215, 1939
- McNaught, J B, Beard, R R, and DeEds, F Effects of Sulfanilamide, Phenothiazine and Thionol in Experimental Trichinosis, *Proc Soc Exper Biol & Med* **41** 17, 1939
- Mahoney, J F, Van Slyke, C J and Thayer, J D Sulfanilamide Therapy in Hospitalized Gonorrhoea, *Am J Syph, Gonorr & Ven Dis* **22** 691, 1938
- Major, R H, and Leger, L H Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, *J A M A* **111** 1919 (Nov 19) 1938
- Maraun, L Zur Prontosilbehandlung des Erysipelas und der Pyurie, *Kinderarztl Praxis* **7** 445, 1936
- Marinkovitch, R Chemotherapy of Gonorrhoea, *Brit M J* **1** 317, 1939
- Marshall, E K, Jr Bacterial Chemotherapy The Pharmacology of Sulfanilamide, *Physiol Rev* **19** 240, 1939
- Cutting, W C, and Cover, A Absorption and Excretion of Certain Sulfanilamide Derivatives, *Bull Johns Hopkins Hosp* **63** 318, 1938
- Emerson, K, and Cutting, W C Para-Aminobenzenesulfonamide Its Absorption and Excretion, Method of Determination in Blood and Urine, *J A M A* **108** 953 (March 10) 1937

- and Long, P H Intravenous Use of Sodium Sulfapyridine, *ibid* **112** 1671 (April 29) 1939
- and Walzl, E M On Cyanosis from Sulfanilamide, *Bull Johns Hopkins Hosp* **61** 140, 1937
- Marvin, H P, and Wilkinson, W E Gonococcic Meningitis Results of Treatment with Sulfanilamide, *J A M A* **110** 800 (March 12) 1938
- Massell, B F, and Jones, T D Effect of Sulfanilamide on Rheumatic Fever and Chorea, *New England J Med* **218** 876, 1938
- May, H B, and Buck, S C Action of the Sulphonamides in Experimental Anthrax, *Lancet* **2** 685, 1939
- Maybaum, J A, Snyder, E R, and Coleman, L L The Value of Sulfanilamide in Orogenous Infections with Special Reference to Its Masking Effect, *J A M A* **112** 2589 (June 24) 1939
- Meissner, W Erfahrungen mit Prontosil bei der Behandlung von entzündlichen Erkrankungen der ableitenden Harnwege, *Med Klin* **33** 95, 1937
- Mellon, R R New Observations on Mechanism of Sulfanilamide's Action Phenomenon of Potentiation, *M Rec* **146** 247, 1937
- Gross, P, and Cooper, F B Sulfanilamide Therapy of Bacterial Infections, Springfield, Ill, Charles C Thomas, Publisher, 1938
- Shinn, L E, and McBroom, J Therapy of Experimental Staphylococcus Infections with Sulfonamide Compounds, *Proc Soc Exper Biol & Med* **37** 563, 1937
- Melton, G, and Beck, A Therapeutic Action of M & B 693 in Urinary Infections, *Lancet* **1** 867, 1939
- Mendell, T H Staphylococcic Septicemia A Review of Thirty-Five Cases, with Six Recoveries, Twenty-Nine Deaths and Sixteen Autopsies, *Arch Int Med* **63** 1068 (June) 1939
- Menefee, E E, Jr, and Poston, M A Effects of Sulfanilamide on *Brucella melitensis*, Var *Melitensis*, *Abortus*, and *Suis*, *J Bact* **37** 269, 1939
- Mergelsberg and Grumer Todesfall nach Ultron, *Dermat Wchnschr* **107** 840, 1938
- Mertins, P S, and Mertins, P S, Jr Meningitis Due to the Type IV Pneumococcus, with Recovery Report of a Case, *Arch Otolaryng* **25** 657 (June) 1937
- Meyer, K A, and Amtman, L Treatment of Friedlander's Septicemia by Sulfapyridine with Recovery, *J A M A* **113** 1641 (Oct 28) 1939
- Michels, M W Sulfanilamide in Treatment of Gonorrheal Ophthalmia in Children, *J Pediat* **13** 527, 1938
- Michie, A M, and Webster, M H Gonococcal Ophthalmia Treated with 2-(p-Aminobenzene sulphonamido) Pyridine, *Lancet* **2** 373, 1938
- Miller, E M, and Fell, E H Sulfanilamide Therapy in Actinomycosis, *J A M A* **112** 731 (Feb 25) 1939
- Montestruc, E Essais de traitement des streptococcies expérimentales du rat et du lapin par injections sous-cutanées, *Bull Soc path exot* **30** 265, 1937
- Muether, B O, and Kinsella, R A Sulfanilamide in the Treatment of Experimental Endocarditis, *J A M A* **110** 603 (Feb 19) 1938
- Mull, J W, and Smith, J T Effect of Sulfanilamide on the Oxygen Capacity of the Blood, *J A M A* **110** 439 (Feb 5) 1938
- Muraz, G, Chirle, H, and Queguener, A Essais comparés de traitements (serum, corps azoïques, sulfanilamide) de la meningite cerebro-spinale, *Presse med* **46** 1113, 1938

- Neal, J B Treatment of Acute Infections of the Central Nervous System with Sulfanilamide, *J A M A* **111** 1353 (Oct 8) 1938
- and Applebaum, E Experience with Sulfanilamide in Meningitis, *Am J M Sc* **195** 175, 1938
- Nelson, A A Histopathological Changes in Hens and Rabbits Following Administration of Sulfanilamide and Sulfanilyl Sulfanilamide, *Pub Health Rep* **54** 106, 1939
- Nelson, J, Rinzler, H, and Kelsey, M P Sulfanilamide Treatment of Erysipelas, *J A M A* **112** 1044 (March 18) 1939
- Newman, C Z Treatment of Undulant Fever with Prontosil, *Brit M J* **2** 342, 1938
- Nichol, C G Treatment of Broncho-Pneumonia in Infants, with M & B 693, *Lancet* **2** 1544, 1938
- Nicol, H, and Freedman, B Fatal Agranulocytosis Following Treatment with M & B 693, *Lancet* **2** 647, 1939
- O'Brien, E J, and McCarthy, C J Staphylococcal Septicaemia Treated with M & B 693, *Lancet* **2** 1232, 1938
- O'Crowley, C R, James, W L, and Sutton, H L Sulfanilyl-Sulfanilamide in the Treatment of Gonorrhea in the Male, *J Urol* **41** 51, 1939
- Ornstein, A M, and Furst, W Peripheral Neuritis Due to Sulfanilamide *J A M A* **111** 2103 (Dec 3) 1938
- Orr, H Sulfanilamide in Treatment of Gonorrhea, *Canad M A J* **37** 364, 1937
- Osgood, E E, and Brownlee, J E Culture of Human Marrow Studies on the Mode of Action of Sulfanilamide, *J A M A* **110** 349 (Jan 29) 1938
- and Powell, H M Failure of Sulfanilamide to Inactivate Preformed Hemotoxins, Diphtheria Toxin, or Tetanal Toxin, *Proc Soc Exper Biol & Med* **39** 37, 1938
- Ottenberg, R, and Fox, C L Explanation for the Cyanosis of Sulphanilamide Therapy, *Proc Soc Exper Biol & Med* **38** 479, 1938
- Pakenham-Walsh, R, and Rennie, A T Sulphonamides in Malaria, *Lancet* **2** 79, 1938
- M & B 693 in Malaria, *ibid* **1** 1382, 1939
- Palazzoli, M, Nitti, F, Bovet, D, and Levinson, M Recherches experimentales concernant l'action du p-aminophenylsulfamide sur la spermatogenese du lapin, *Compt rend Soc de biol* **128** 261, 1938
- Pariser, H The Use of Prontylin in Seroresistant Syphilis, *Am J Syph, Gonorr & Ven Dis* **24** 48, 1940
- Paton, J P, J, and Eaton, J C Sulphaemoglobinaemia and Methaemoglobinemia Following Administration of p-Aminobenzenesulphonamide, *Lancet* **1** 1159, 1937
- Pepper, D S, Flippin, H F, Schwartz, L, and Lockwood, J S The Results of Sulfapyridine Therapy in Four-Hundred Cases of Typed Pneumococcal Pneumonia, *Am J M Sc* **198** 22, 1939
- Pernice, W Ueber die Behandlung der kindlichen Pyurie mit Prontosil, *Kinderarztl Praxis* **7** 304, 1936
- Peters, B A, and Howard, R V Chemotherapy of Streptococcal Infections with p-Benzylamino-Benzene-Sulfonamide, *Lancet* **1** 1273, 1937
- Pittman, M The Protection of Mice Against Hemophilus Influenzae (Non-Specific) with Sulfapyrine, *Pub Health Rep* **54** 1769, 1939
- Plummer, N, and Ensworth, H Preliminary Report of Use of Sulfapyridine in Treatment of Pneumonia, *Bull New York Acad Med* **15** 241, 1939

- Sulfapyridine in the Treatment of Pneumonia, *J A M A* **113** 1847 (Nov 18) 1939
- Porter, J R, and Hale, W M Effect of Sulfanilamide and Sulfapyridine on Experimental Infections with *Listerella* and *Erysipelothrix* in Mice, *Proc Soc Exper Biol & Med* **42** 47, 1939
- Poulton, E P Discussion on Sulphanilamide and Its Congeners, *Brit M J* **2** 929, 1937
- Powell, H M, and Jamieson, W A Combined Therapy of Pneumococcic Rat Infections with Rabbit Antipneumococcic Serum and Sulfapyridine, *J Immunol* **36** 459, 1939
- Prebble, E E Treatment of Acute Gonorrhoea with M & B 693, *Lancet* **2** 1163, 1938
- Price, A E, and Myers, G B Treatment of Pneumococcic Pneumonia with Sulfanilamide, *J A M A* **112** 1021 (March 18) 1939
- Proom, H The Therapeutic Action of p-Aminobenzene Sulphonamide in Meningococcal Infection of Mice, *Lancet* **1** 16, 1937
- Punch, A L Undulant Fever Treated with Prontosil, *Lancet* **2** 429, 1938
- Purdie, A W, and Fry, R M Chronic Haemolytic Streptococcal Infection Treated with p-Aminobenzenesulphonamide, *Lancet* **2** 18, 1937
- Raiziss, G W, Severac, M, Moetsch, J C, and Clemence, L W Chemotherapeutic Studies on Sulfamidyl (Para-Amino-Benzene-Sulfonamide) In Experimental Beta-Hemolytic Streptococcic Infection, *J Chemotherapy* **14** 1, 1937
- The Chemotherapy of Sulfanilamide, Prontosil Soluble, Di-Sulfanilamide and Proseptasine, *ibid* **14** 91, 1938
- Therapeutic Effects of 4, 4'-Diamino-Diphenyl-Sulfone, Corresponding Sulfide and Acetyl Derivatives in Streptococcic Infection, *Proc Soc Exper Biol & Med* **39** 339, 1938
- Comparative Effects of Sulfapyridine and Sulfanilamide in Type II Pneumococcic Infection of Mice, *ibid* **40** 434, 1939
- Protective Effect of Sulfapyridine, Sodium Sulfapyridine, and Sulfanilamide in *Pneumococcus* Types I, II and III, *ibid* **42** 12, 1939
- Raman, P S Pneumococcal Meningitis Treated with M & B 693, *Lancet* **1** 1101, 1939
- Reid, G C K, and Dyke, S C Pneumococcal Meningitis Treated with M & B 693 Recovery, *Lancet* **2** 619, 1938
- Reid, R D Observations on the Mode of Action of Sulfapyridine on *Pneumococcus*, *Proc Soc Exper Biol & Med* **41** 437, 1939
- Reuter, F A Use of Sulfanilamide in Treatment of Gonorrhoea Report of Results in One Hundred Cases, *M Ann District of Columbia* **6** 115, 1937
- Rich, A R, and Folis, R H Inhibitory Effect of Sulfanilamide on Development of Experimental Tuberculosis in Guinea Pig, *Bull Johns Hopkins Hosp* **62** 77, 1938
- Richardson, L A Infection with *Brucella Abortus* Treated with Prontosil *Lancet* **1** 495, 1938
- Rimington, C, and Hemmings, A W Porphyrinuria Following Sulphanilamide Sulphanilamide Dermatitis, *Lancet* **1** 770, 1938
- Robertson, K Case of Pneumococcal Meningitis Treated with M & B 693, *Lancet* **2** 728, 1938
- Roche, E H, and Caughey, J E "Influenzal" Meningitis Treated with M & B 693 Report on Two Cases, *Lancet* **2** 635, 1939

- Rosenthal, S M Studies in Chemotherapy Chemotherapy of Experimental Pneumococcus Infections, Pub Health Rep **52** 48, 1937
- Studies in Chemotherapy Comparative Studies in Experimental Pneumococcus, Streptococcus and Meningococcus Infections, *ibid* **52** 662, 1937
- Ross, R W Acquired Tolerance of Pneumococcus to M & B 693, Lancet **1** 1207, 1939
- Ruesegger, J M, and Hamburger, M Effect of Sulfanilamide on Pneumococcal Infections in Mice, J Infect Dis **64** 18, 1939
- Sadusk, J F, Jr, and Manahan, C P Sulfanilamide for Puerperal Infections Due to Clostridium Welchii, J A M A **113** 14 (July 1) 1939
- Sailei, S Subacute Bacterial Endocarditis Treated with Sulfanilamide Resulting in Granulocytopenia and Death, Am J Clin Path **9** 269, 1939
- Sako, W, Dwan, P F, and Platou, E S Sulfanilamide and Serum in the Treatment and Prophylaxis of Scarlet Fever, J A M A **111** 995 (Sept 10) 1938
- Saphirstein, H Hepatitis and Toxic Erythema with Desquamation Due to Sulfanilamide, Urol & Cutan Rev **42** 101, 1938
- Sappington, S W, and Favorite, G O Sulfanilamide and Meningitis, Ann Int Med **13** 576, 1939
- Schmidt, J Ein Beitrag zur Prontosilbehandlung bei septischen und ähnlichen Eikrankungen, Munchen med Wchnschr **83** 2122, 1936
- Schmidt, L H Use of Sulfanilamide in the Treatment of Type XIV Pneumococcus Infections in Mice, Proc Soc Exper Biol & Med **37** 205, 1937
- Schianz, H Zur Sepsisbehandlung mit Prontosil, Munchen med Wchnschr **82** 419, 1935
- Schutze, H Chemotherapy in Plague Infection, Lancet **1** 226, 1939
- Schwartz, L, Flippin, H F, and Turnbull W G Treatment of Pneumococcal Pneumonia A Comparative Study of Three Hundred and Fifty-One Patients Treated at the Philadelphia General Hospital, Ann Int Med **13** 1005, 1939
- Schwartz, W F, Garvin, C F, and Koletsky, S Fatal Granulocytopenia from Sulfanilamide, J A M A **110** 368 (Jan 29) 1938
- Schwentker, F F, in discussion on Bliss, E A, and Long, P H Observations on the Mode of Action of Sulfanilamide, J A M A **109** 1527 (Nov 6) 1937
- Clason, F P, Morgan, W A, Lindsay, J W, and Long, P H Use of Para-Aminobenzenesulphonamide or Its Derivatives in Treatment of Beta Hemolytic Streptococcal Meningitis, Bull Johns Hopkins Hosp **60** 297, 1937
- Scott, G A, and Meerapfel, O The Effect of Sulphonamides on Blood-Serum, Lancet **2** 244, 1939
- Shaffer, L W, and Arnold, E Lymphogranuloma Venereum, Especially Its Treatment with Sulfanilamide, Arch Dermat & Syph **38** 705 (Nov) 1938
- Shelley, H A Report on the Treatment of Gonococcal Urethritis with Sulfanilamide, Bull School Med Univ Maryland **23** 123, 1939
- Shinn, L E, Main, E R, and Mellon, R R Anticatalase Activity of Sulfanilamide and Related Compounds I Effect of Ultraviolet Radiation, Proc Soc Exper Biol & Med **39** 272, 1938
- Anticatalase Activity of Sulfanilamide and Related Compounds II Relation to Growth Inhibition in Pneumococcus, *ibid* **39** 591, 1938
- Shiopshear, G Sulfanilamide in Treatment of Strictures of Rectum Caused by Lymphogranuloma Venereum Preliminary Report, Illinois M J **74** 97, 1938
- Silver, B, and Elliott, M Use of Sulfanilamide in 1,625 Cases of Gonorrhea in the Male, J A M A **112** 723 (Feb 25) 1939
- Smith, A Chemotherapy of Streptococcal Infections, Lancet **2** 1064, 1937

- Smith, C H, and Nemir, R E The Sulfapyridine Treatment of Pneumonia in Children, *J A M A* **113** 1857 (Nov 18) 1939
- Smith, F J, and Needles, R J Report of Fifty Cases of Acute Lobar Pneumonia in Adults Treated with Sulfapyridine, *Am J M Sc* **198** 19, 1939
- Smith, F W, Mayer, K F, Agerty, H A, Fowler, R H, and Layton, W C Anaerobic Beta Hemolytic Streptococcus Meningitis of Otic Origin Treated with Sulfanilamide and Culminating in Complete Recovery, *J A M A* **110** 887 (March 19) 1938
- Smith, H B, and Coon, E H Meningitis Due to Hemolytic Streptococcus Report of Two Cases with Recovery After the Use of Prontosil and Sulfanilamide, *Arch Otolaryng* **26** 56 (July) 1937
- Smith, K M, and Curtis, A C Brucellosis with Sulfanilamide Report of a Case with Failure of Sulfanilamide Therapy, *Am J M Sc* **198** 342, 1939
- Smith, W H Y, Weil, C K, and Bird, B C Sulfanilamide in Gonococcal Infection Results of Treatment and Leukocyte Response, *Ven Dis Inform* **20** 119, 1939
- Smithburn, K C Inefficacy of Prontylin in Experimental Tuberculosis, *Proc Soc Exper Biol & Med* **38** 574, 1938
- Snodgrass, W R, and Anderson, T Prontosil in Treatment of Erysipelas Controlled Series of Three Hundred and Twelve Cases, *Brit M J* **2** 101, 1937
- Sulphanilamide in Treatment of Erysipelas Controlled Series of Two Hundred and Seventy Cases, *ibid* **2** 1156, 1937
- and Rennie, J L Sulphamido-Chrysoidine, Sulphanilamide and Benzyl-Sulphanilamide in Treatment of Erysipelas Controlled Series of Two Hundred and Forty-Two Cases, *ibid* **2** 399, 1938
- Somers, R B U M & B 693 in Cerebrospinal Fever A Review of One Hundred and Forty-Three Cases Treated Under Field Conditions, *Lancet* **1** 921, 1939
- Southworth, H, and Cooke, C Hematuria, Abdominal Pain and Nitrogen Retention Associated with Sulfapyridine, *J A M A* **112** 1820 (May 6) 1939
- Spearmen, M P, and Vandevere, W E Sulfapyridine in Trachoma, *J A M A* **113** 1807 (Nov 11) 1939
- Speert, H Passage of Sulfanilamide Through Human Placenta, *Bull Johns Hopkins Hosp* **63** 337, 1938
- Spink, W W, and Crago, F H Evaluation of Sulfanilamide in the Treatment of Patients with Subacute Bacterial Endocarditis, *Arch Int Med* **64** 228 (Aug) 1939
- Stamp, T C Bacteriostatic Action of Sulphanilamide in Vitro Influence of Fractions Isolated from Haemolytic Streptococci, *Lancet* **2** 10, 1939
- Stannus, H S, and Findlay, G M Monocytic Angina (Glandular Fever) Treated with M & B 693, *Lancet* **2** 595, 1939
- Steinbach, M M, and Dillon, B M Sulfanilamide in Experimental Tuberculosis, *Proc Soc Exper Biol & Med* **41** 613, 1939
- Stern, R L, and Blake, K W Undulant Fever Its Treatment with Sulfanilamide, *J A M A* **110** 1550 (May 7) 1938
- Stewart, H L, and Pratt, J P Sulfanilamide Excretion in Human Breast Milk and the Effect on Breast-Fed Babies, *J A M A* **111** 1456 (Oct 15) 1938
- Stewart, J D, Rourke, G M, and Allen, J G Excretion of Sulfanilamide, *J A M A* **110** 1885 (June 4) 1938
- Stewart, W, and Bates, T Bacillus Pyocyaneus Infections A Case Treated with Sulphanilamide, *Lancet* **1** 820, 1939
- Stokinger, H E Absorption, Acetylation, and Excretion of 2 Sulfanilamido Pyridine (Dagenan, M & B 693), *Proc Soc Exper Biol & Med* **40** 61, 1939

- Strickler, A, and Stone, M J Sulfanilamide in Treatment of Pyogenic Dermatoses, *Arch Dermat & Syph* **40** 244 (Aug) 1939
- Sutherland, M E Agranulocytosis Following Administration of M and B 693, *Lancet* **1** 1208, 1939
- Swift, H F, Moen, J K, and Hirst, G K Action of Sulfanilamide in Rheumatic Fever, *J A M A* **110** 426 (Feb 5) 1938
- Tedder, J W Toxic Manifestations in Skin Following Sulfanilamide Therapy, *Arch Dermat & Syph* **39** 217 (Feb) 1939
- Thomas, C B, and France, R Preliminary Report of Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *Bull Johns Hopkins Hosp* **64** 67, 1939
- Thompson, A R, and Greenfield, C R M Chemotherapy in Measles and Whooping-Cough Prophylaxis and Treatment of Complications, *Lancet* **2** 991, 1938
- Thornhill, W A, Jr, Swart, H A, and Reel, C Sulfanilamide in Staphylococcal Septicemia, *J A M A* **113** 1638 (Oct 28) 1939
- Toomey, J A, and Kimball, E R, Jr Meningitis Caused by *Streptococcus Haemolyticus* and Treated with Sulfanilamide, *J A M A* **112** 2586 (June 24) 1939
- and Takacs, W S Mephanyl Borate and Sulfanilamide in Experimental Poliomyelitis, *Arch Pediat* **55** 307, 1938
- Sulfapyridine (Dagenan) and Experimental Poliomyelitis, *ibid* **56** 384, 1939
- Toone, E C, and Jenkins, A M Undulant Fever (Brucellosis) Treated with Sulfanilamide Report of Case with Recovery, *South M J* **31** 478, 1938
- Topping, N H Experimental Rocky Mountain Spotted Fever and Endemic Typhus Treated with Prontosil or Sulfapyridine, *Pub Health Rep* **54** 1143, 1939
- Trachler, W H, Frauenberger, G S, Wagner, C, and Mitchell, A G Streptococcal Meningitis with Special Emphasis on Sulfanilamide Therapy, *J Pediat* **11** 248, 1937
- Traut, E F, and Logan, C E Undulant Fever Treated with Sulfanilamide, *J A M A* **111** 1092 (Sept 17) 1938
- Trefouel, J, Trefouel, J (Mme), Nitti, F, and Bovet, D Activite du p-aminophenylsulfamide sur les infections streptococciques experimentales de la souris et du lapin, *Compt rend Soc de biol* **120** 756, 1936
- Troup, A G, and White, R M Pemphigus Neonatorum Treated with Sulfapyridine (M & B 693), *Lancet* **2** 1367, 1939
- Tsao, Y F, McCracken, M E, Chen, J, Kuo, P T, and Dale, C L Renal Complication in Sulfapyridine Therapy Report of Five Cases with One Death, *J A M A* **113** 1316 (Sept 30) 1939
- Tunnichiff, R The Action of Prontosil-Soluble and Sulfanilamide on the Phagocytic Activity of Leukocytes and on the Dissociation of Streptococci, *J Infect Dis* **64** 59, 1939
- Van Dyke, H B, Greep, R O, Rake, G, and McKee, C M Observations on the Toxicology of Sulfathiazole and Sulfapyridine, *Proc Soc Exper Biol & Med* **42** 410, 1939
- Vigoni, M Au sujet de l'action des derives sulfamides sur la spermatogenese, *J belge d'uro* **11** 375, 1938
- Wade, H J Staphylococcal Septicemia Treated with M & B 693, *Lancet* **1** 756, 1939
- Waghelstein, J M Sulfanilamide in the Treatment of One Hundred and Six Patients with Meningococcal Infections, *J A M A* **111** 2172 (Dec 10) 1938

- Wagner, J C Anterior Poliomyelitis Treated with Sulfapyridine, *J A M A* **112** 1934 (May 13) 1939
- Walker, K , Sigetti, C W , and Wiesner, B P Effects of Sulphanilamide on Fertility, *Lancet* **2** 1491, 1938
- Walker, O Sulphanilamide in the Treatment of Actinomycosis, *Lancet* **1** 1219, 1938
- Walzak, B J Sulfanilamide and Sulfanilyl-Sulfanilamide in Gonococcus Infections, *Am J Syph, Gonor & Ven Dis* **23** 597, 1939
- Weidekamp, M Zur Behandlung der Mischinfizierten Knochentuberkulose und der Osteomyelitis mit Prontosil, *Deutsche med Wchnschr* **64** 854, 1938
- Welch, H , Wentworth, J A , and Mickle, F L Use of Sulfanilamide in the Diagnosis and Treatment of Brucellosis, *J A M A* **111** 226 (July 16) 1938
- Wendel, W B Use of Methylene Blue in Methemoglobinemia from Sulfanilamide Poisoning, *J A M A* **109** 1216 (Oct 9) 1937
- Whitby, L Chemotherapy of Bacterial Infections, *Lancet* **2** 1095, 1938
- Whitby, L E H Chemotherapy of Pneumococcal and Other Infections, *Lancet* **1** 1210, 1938
- Chemotherapy of Bacterial Infections, *ibid* **2** 1095, 1938
- Wien, R Toxicity of 2-(*p*-Aminobenzenesulphonamido) Pyridine, *Quart J Pharm & Pharmacol* **11** 217, 1938
- Wigton, R S , and Johnson, S H Peripheral Neuritis Following Sulfanilyl Sulfanilamide (Disulfanilamide) Report of Four Cases, *J A M A* **111** 1641 (Oct 29) 1938
- Wilkie, C H Treatment of Gonorrhea by Uleron Review of One Hundred and Twenty Male Cases, *Brit M J* **1** 57, 1939
- Willien, L J Sulfanilamide Therapy in Meningococcus Meningitis, *J A M A* **110** 630 (Feb 26) 1938
- Willis, T Sulfanilamide in Ophthalmia Neonatorum, *Yale J Biol & Med* **10** 275, 1938
- Wilson, A T , Spreen, A H , Cooper, M L , Stevenson, F E , Cullen, G E , and Mitchell, A G Sulfapyridine in Treatment of Pneumonia in Infants and Children, *J A M A* **112** 1435 (April 15) 1939
- Wilson, J F Sulfanilamide in Treatment of Acute Lupus Erythematosus Failure with Well Controlled Administration, *Arch Dermat & Syph* **40**.241 (Aug) 1939
- Wood, W G Anemia During Sulfanilamide Therapy, *J A M A* **111** 1916 (Nov 19) 1938
- Young, C J Agranulocytosis and Para-Amino-Benzene Sulphonamide, *Brit M J* **2** 105, 1937
- Young, F Pneumococcal Meningitis Treated with Sulphanilamide Recovery, *Brit M J* **2** 286, 1938
- Young, R H , and Moore, C Influenzal Meningitis Report of Case Treated with Anti-Influenzal Serum and Sulphanilamide, *Arch Pediat* **55** 282, 1938
- Zaytzeff-Jern, H , and Meleney, F L Effect on Bacteriophage of Prontylin, Prontosil, Sulfapyridine and Other Antiseptics and Dyes Used in Surgical Practice, *J Lab & Clin Med* **24** 1017, 1939
- Zendel, J F , and Greenberg, D Meningococccmia Treatment with Sulfanilamide and Prontosil, Report of Two Cases, *New York State J Med* **37** 1744, 1937

EFFECT OF SULFANILAMIDE ON FIBRINOLYTIC ACTIVITY OF HEMOLYTIC STREPTOCOCCI

LAURENCE E HINES, M D

ALLEN H HOOVER, M D

AND

EDWIN GRAFF, B S

CHICAGO

In 1933 Tillett and Garner¹ demonstrated in cultures of hemolytic streptococci a freely excreted extracellular substance which had the property of dissolving solid human fibrin. They also reported that the fibrin from patients recently recovered from hemolytic streptococcal infections often became completely resistant to the fibrinolytic action of hemolytic streptococci. As a result of early observations in this field it was believed that the reaction was a specific immunity response, because patients who had recovered from nonstreptococcal infections did not show this antifibrinolytic reaction. This view is now known to be erroneous, because subsequent investigations by Wadler,² Harris³ and others have demonstrated resistance to fibrinolysis in a small percentage of normal persons and in a large percentage of patients with pneumonia or other infection.

In preliminary studies of normal persons and of patients with various types of infection we were able to demonstrate the fibrinolytic activity of many strains of hemolytic streptococci. Also an antifibrinolytic reaction occurred in several patients who had various types of severe infections. The present study of the effect of sulfanilamide on fibrinolysis was stimulated by the observations in 1 patient in whom hemolytic streptococcal pneumonia developed during a period when he was receiving sulfanilamide. At the beginning of the experiment the man had no evidence of infection, and his blood fibrin was dissolved in normal

From the Department of Medicine, Northwestern University Medical School, and St Joseph Hospital

1 Tillett, W C, and Garner, R L. The Fibrinolytic Activity of Hemolytic Streptococci, *J Exper Med* **58** 485 (Oct) 1933

2 Wadler, E. Development of Antifibrinolytic Properties in Blood of Patients with Rheumatic Fever, *J Clin Investigation* **16** 145, 1937

3 Harris, C H S. Hemolytic Streptococcal Fibrinolysis, *Brit J Exper Path* **16** 513, 1935

time by a strain of hemolytic streptococcus. Forty-eight hours later pneumonia developed suddenly, with chill, fever, pulmonary consolidation and blood-tinged sputum containing hemolytic streptococci. On the first day of the infection the blood sulfanilamide level was only 3.5 mg per hundred cubic centimeters, and the fibrinolysis time was not appreciably increased. The dose of sulfanilamide was increased, and within forty-eight hours symptoms of infection had disappeared, the blood sulfanilamide had reached 6.2 mg per hundred cubic centimeters, and antifibrinolysins had developed. These observations suggested that sulfanilamide might have some effect on the inhibition of fibrinolysis and prompted this study. *In vitro* experiments by Huntington,⁴ however, have shown that fibrinolysis was not affected when sulfanilamide was added in a concentration equal to that found in the body fluids of patients treated adequately by the drug. For this reason and because the fibrin of laboratory animals is naturally resistant to lysis by hemolytic streptococci, our experiments were performed on patients without demonstrable infection.

METHOD

Patients who were normal as far as temperature, leukocyte count and sedimentation rate were concerned were selected as subjects. Preliminary fibrinolysin experiments were made, and patients with a liquefaction time of more than four hours were rejected. Many of the patients in whom mild toxic symptoms developed refused to allow the experiment to be concluded. In 9 experiments in which sulfanilamide was used in therapeutic doses the liquefaction time for each subject's plasma fibrin was determined by a modification of the method of Todd and Garner which was described by Hadfield, Magee and Perry.⁵ The same strain of hemolytic streptococci of the same incubation age was used to test both preliminary and subsequent fibrinolysin time on each patient. Because the fibrinolytic activity of some strains is known to diminish with age, control tests of the organism against normal plasma fibrin were carried out. The source of the streptococci, all of beta hemolytic type, is shown in charts 1 to 9. Sulfanilamide determinations in the blood were made according to Marshall's method.⁶

RESULTS

The essential details of the observations are shown in the charts. An increased resistance to fibrinolysis occurred in all patients who

4 Huntington, R. W. Failure of Sulphanilamide to Prevent Hemolysis, Fibrinolysis and Production of Erythrogenic Toxin by Hemolytic Streptococci *in Vitro*, *Proc Soc Exper Biol & Med* **38** 328, 1938.

5 Hadfield, G., Magee, V., and Perry, C. B. Lysis of Fibrin by Streptococci, *Lancet* **1** 834, 1934.

6 Marshall, E. K., Jr. Determination of Sulphanilamide in Blood and Urine, *Proc Soc Exper Biol & Med* **36** 422, 1937.

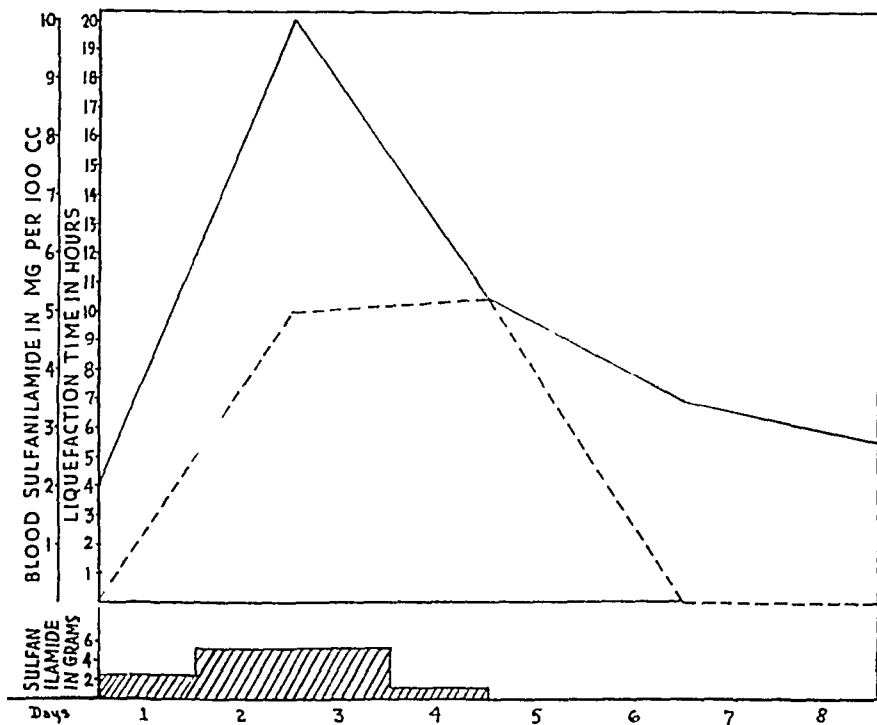


Fig 1—G O, aged 24 (diagnosis old cerebral concussion), received 10.6 Gm of sulfanilamide in the first forty-eight hours. The liquefaction time was twenty-four hours, went down to ten and one-half hours in the next two days with the blood sulfanilamide only slightly increased and returned to its normal level after administration of sulfanilamide was stopped. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

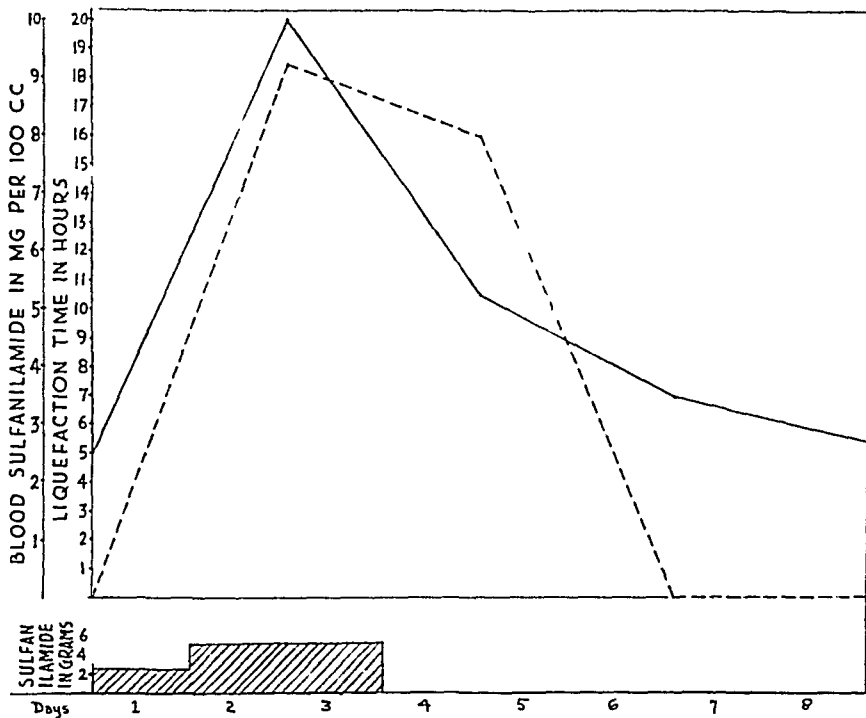


Fig 2—T H, aged 28 (diagnosis healed duodenal ulcer), had the highest concentration of blood sulfanilamide 9.2 mg per hundred cubic centimeters in forty-eight hours. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

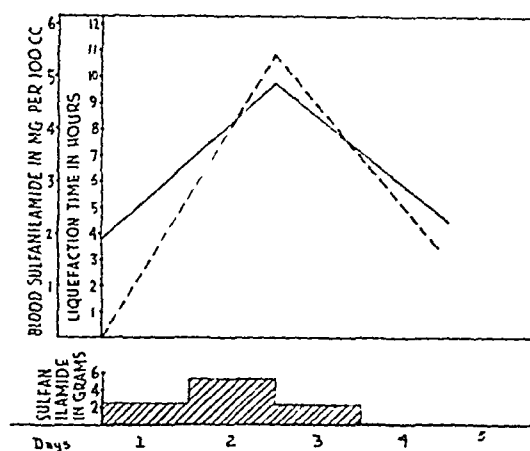


Fig 3—F E, aged 50 (diagnosis tumor of colon), had a gastric hemorrhage on the third day, and administration of sulfanilamide was stopped. The total amount of sulfanilamide administered was 10.6 Gm. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

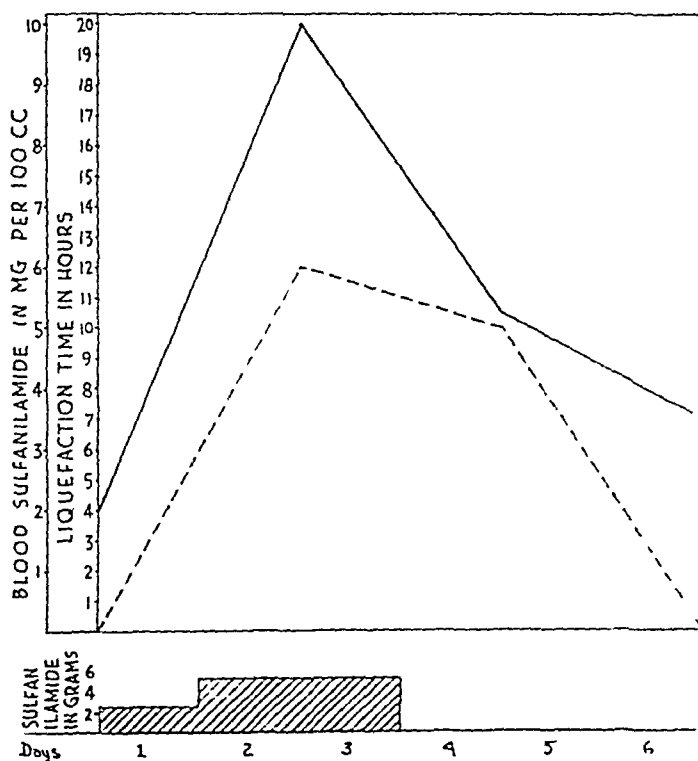


Fig 4—R E, aged 27 (diagnosis neurasthenia), had a sulfanilamide concentration of 6 mg per hundred cubic centimeters of blood, with a liquefaction time of twenty hours on the second day. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

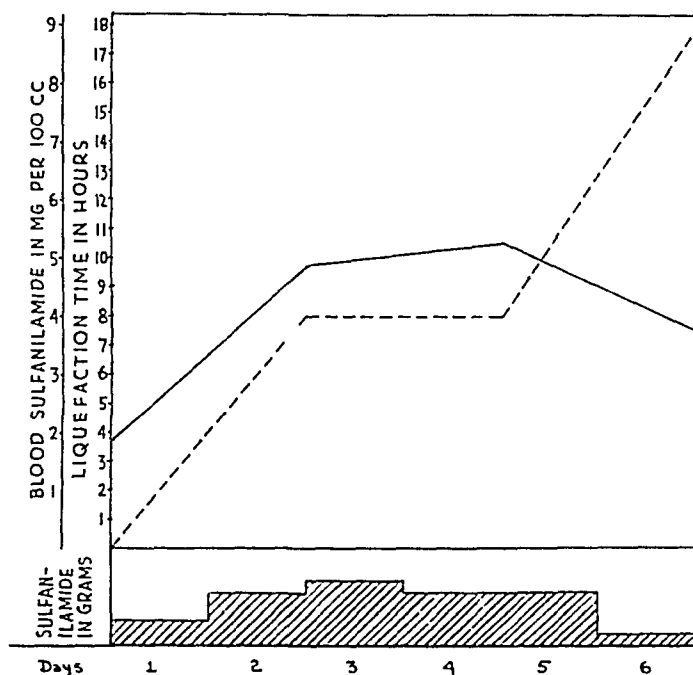


Fig 5—H E, aged 46 (diagnosis deviation of nasal septum), had a liquefaction time which paralleled the first increase of blood sulfanilamide and dropped slightly on the fifth day, with the blood sulfanilamide concentration rising to 9 mg per hundred cubic centimeters. The broken line represents values of blood sulfanilamide, the unbroken line, liquefaction time.

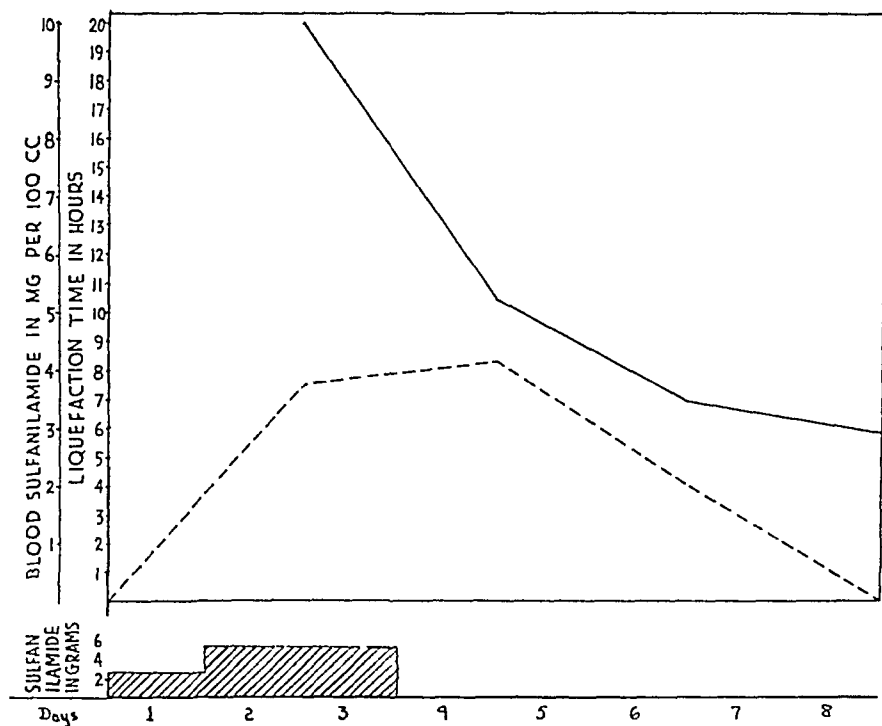


Fig 6—J O, aged 39 (fracture of the right hip), whose control specimen for liquefaction clotted spontaneously, had a liquefaction time of twenty hours after the administration of 13.3 Gm of sulfanilamide. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

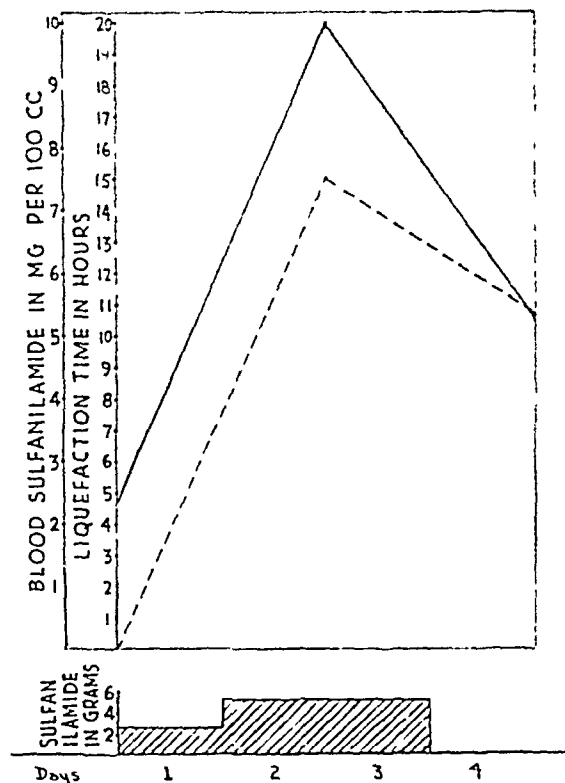


Fig 7—S C, aged 50, was hospitalized for treatment of hammer toe. The liquefaction time (rising to twenty hours) paralleled the blood sulfanilamide concentration. On the fourth day a heart attack developed and the patient died suddenly. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

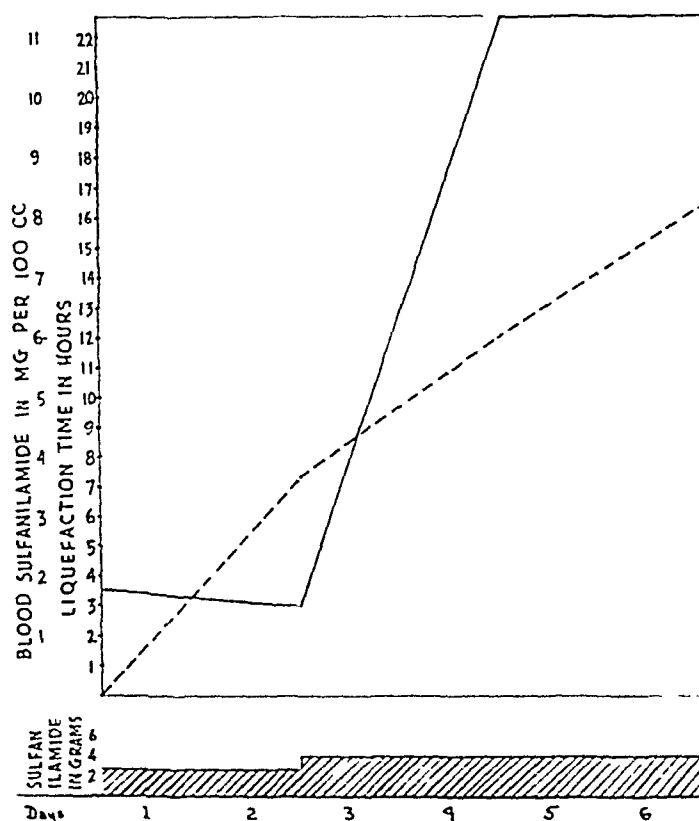


Fig 8—W I, aged 48, had hemiplegia and was taking 4 Gm of sulfanilamide daily. Streptococcic pneumonia developed on the second day. Liquefaction time was slightly accelerated and subsequently was prolonged to twenty-four hours with recovery. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

received therapeutic doses of sulfanilamide. The highest blood sulfanilamide level of the series was 9.2 mg per hundred cubic centimeters, the lowest, 4.2 mg. Even in patients with blood sulfanilamide at the lower levels inhibition of fibrinolysis occurred. Usually the increase or decrease of liquefaction time paralleled the rise or fall of the concentration of sulfanilamide in the blood. The fibrinolysin time returned to its normal level in from two to five days after administration of the drug had been discontinued.

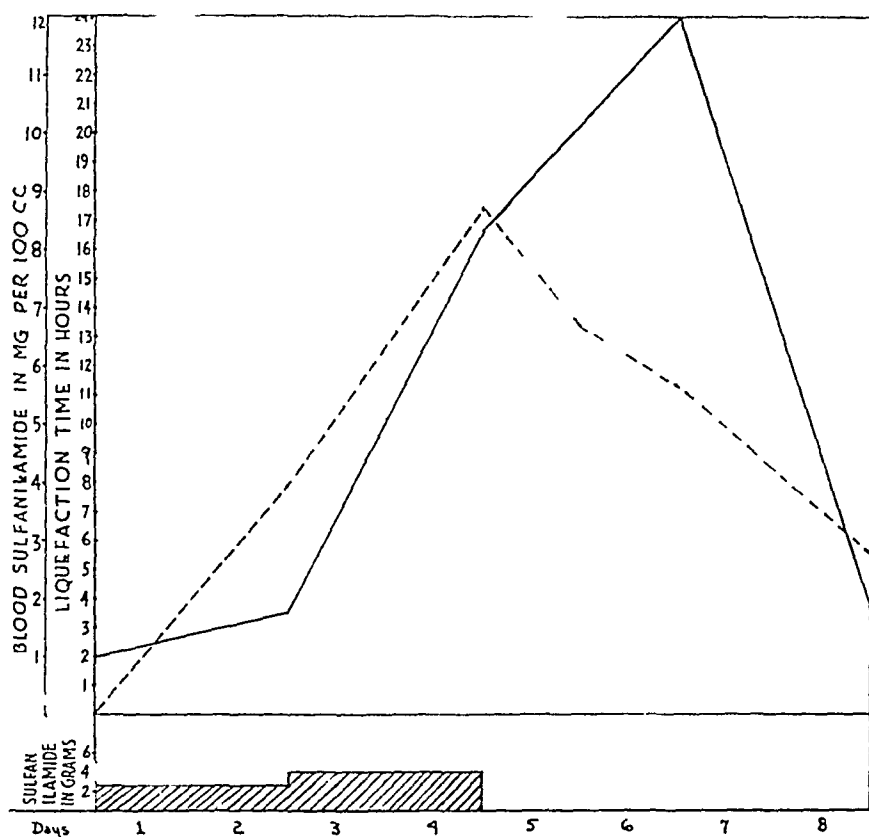


Fig 9—C O, aged 70 (diagnosis old hemiplegia), had a sulfanilamide concentration which reached 8.7 mg per hundred cubic centimeters of blood, paralleling the prolonged liquefaction time. The broken line represents the values of blood sulfanilamide, the unbroken line, liquefaction time.

COMMENT

The mechanism of the action of sulfanilamide as an effective therapeutic agent against infections due to hemolytic streptococci and other agents is not completely known. Little or no bactericidal effect can be demonstrated in the test tube. As Gay and Clark⁷ stated, this fact

⁷ Gay, F, and Clark, A. On the Mode of Action of Sulphanilamide in Experimental Streptococcus Empyema, *J Exper Med* **66** 535, 1937.

at once points to a necessary adjuvant or determinative action on the part of the fluids or cells of the host. They stated the belief that sulfanilamide produces a bacteriostasis sufficiently marked to protect the accumulated leukocytes and to allow the natural defense macrophages to accumulate. Our observations are compatible with this theory. Gay and Clark suggested further that the resistance of fibrin in the plasma to liquefaction by hemolytic streptococci may play a part in such a bacteriostatic reaction. A further speculation is that sulfanilamide prevents the spread of organisms from an infected focus to regional lymphatics or to the blood stream by rendering the fibrin in tissue spaces around the infected focus insusceptible to the lytic action of hemolytic streptococci.

BLOOD PRESSURES IN AORTIC COARCTATION

STUDY OF PULSE CONTOURS TAKEN BY THE DIRECT METHOD

R A WOODBURY, M D, P H D

EUGENE E MURPHEY, M D

AND

W F HAMILTON, P H D

AUGUSTA, GA

Reviews by Abbott¹ and Blackford² have shown that about 300 cases of coarctation of the aorta have been reported. In very few of these cases, however, was the diagnosis made during the life of the patient, and studies of the blood pressure were limited by the methods available for estimating it.³ This communication describes the results of direct optical registration of the blood pressures in various arteries in a case of aortic coarctation when the patient was at rest, during and after temporary occlusion of an artery, coughing and straining, and after administration of epinephrine and of amyl nitrite.

MATERIAL AND METHODS

The subject of these studies, F H, was a Negro, aged 26, of good physical development but of a very low grade of mentality. On admission to the hospital in 1932, his chief complaint was attacks of pain over the heart and in the left shoulder during the previous two years. He also had shortness of breath, which did not hinder either work or sleep, and complained of headache, slight cough and palpitation after exercise.

The skin, central nervous system, abdomen, skeleton and muscular system showed nothing abnormal on routine physical examination. The electrocardiogram,

This investigation was aided by a grant from the American Medical Association.

From the Department of Physiology and Pharmacology and the Department of Medicine, University of Georgia School of Medicine.

1 Abbott, M E. Coarctation of the Aorta of the Adult Type. II. A Statistical Study and Historical Retrospect of Two Hundred Recorded Cases, with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, *Am Heart J* **3** 392, 1928.

2 Blackford, L M. Coarctation of the Aorta, *Arch Int Med* **41** 702 (May) 1928.

3 Blumgart, H L, Lawrence, J S, and Ernstene, A C. Dynamics of the Circulation in Coarctation (Stenosis of Isthmus) of the Aorta of the Adult Type. Relation to Essential Hypertension, *Arch Int Med* **47** 806 (May) 1931.

chemical analysis of the blood, blood count and urinalysis revealed no abnormality. The Wassermann and Kahn tests were negative.

Examination of the chest showed normal lungs. There was a slight bulge of the precordium with a diffuse point of maximal impulse. The apex beat was in the fifth interspace, 10 cm to the left of the midsternal line. No thrills or shocks could be discovered on palpation. The heart was enlarged both to the right and to the left, the right border lying about 4 cm to the right of the midsternal line in the third interspace, and the other border lying about 13 cm to the left in the fifth interspace. The mitral valve showed no abnormality except an accentuated first sound. A loud, blowing systolic murmur was heard over the entire sternum both to the right and to the left in the aortic and pulmonary areas and transmitted downward along the right border of the sternum. This murmur was also transmitted into the arteries of the neck and could be heard in the back just to the right of the seventh cervical vertebra. The arteries seemed to be slightly thickened.

The foregoing observations were made in the course of hospital routine, as carried out by interns and passed by the resident, and gave an impression of congenital heart disease, hypertension and moderate arteriosclerosis.

However, when the patient was properly undressed and examined in a good light a number of points were noted which had been overlooked in the routine examination. First, although there was marked activity of the great vessels of the neck, marked precordial heaving and forcible apex impulse, nevertheless there was no evidence of pulsation in the abdominal aorta on inspection, nor could any pulsation be detected in the femoral arteries. These appearances were substantiated by palpation and auscultation, which revealed a very faint femoral pulse and absence of the sounds ordinarily elicited over the femoral arteries. In addition to this, the left external mammary artery was dilated to the size of a chicken quill and was tortuous and visible throughout its length. The same phenomenon was present to a lesser degree on the right side. There were also numerous dilated arteries along the margin of the sternum and in the intercostal spaces, which were easily discernible. From these observations the diagnosis of coarctation of the aorta was made. A roentgenogram revealed erosions along the margin of the ribs such as were described by Abbott¹ and others.

The patient was readmitted in 1936, his condition was practically unchanged except that both the Wassermann and the Kahn reaction were now positive (4 plus).

It was evident that the syndrome was that of coarctation of the aorta, that the aortic "*Windkessel*" was divided into two segments, one above and one below the coarctation, and that the collateral circulation, while adequate to maintain the health of the lower parts of the body, was at the same time sluggish enough to make possible the separate study of the two reservoirs and their branches.

Methods—Direct simultaneous optical records of the blood pressures were made in branches of the upper and lower arterial systems by means of the hypodermic manometer⁴. This gave an accurate direct measure of the systolic

4 (a) Hamilton, W F, Brewer, G, and Brotman, I. Pressure Pulse Contours in the Intact Animal. I. Analytical Description of a New High Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, *Am J Physiol* **107** 427, 1934. (b) Hamilton, W F, Woodbury, R A, and Harper, H T, Jr. Physiologic Relationships Between Intrathoracic, Intrasplinal and Arterial Pressures, *J A M A* **107** 853 (Sept 12) 1936.

and diastolic pressures of the same pulsation in both systems and of the transmission time and showed details of the pulse contour

The arteries of the arm could be entered with a 22 gage needle by simple puncture through the skin, but pulsations of the femoral and dorsalis pedis arteries were so difficult to palpate that surgical exposure of these vessels was necessary. Incision and puncture were done with the area under local anesthesia.

RESULTS AND DISCUSSION

Pressure Values—The brachial blood pressure as measured directly was 160 mm of mercury systolic and 100 diastolic. With the auscultatory method the values were 164 systolic and 100 diastolic. In the legs the clinical method gave less accurate results (130 systolic and 100 diastolic against the direct reading of 105 systolic and 80 diastolic).

These observations bear out the findings, discussed in detail in other papers from these laboratories,⁵ that variations in the size of the cuff, the size of the limbs, the compressibility of tissue and the pulse contour influence the values obtained by the indirect method. In view of the inaccuracy of auscultatory measurements, all values reported here are those obtained by the direct method. Results are presented in the form of accurate reconstructions of the blood pressure curves. Pressure relationships can be measured to within ± 1 mm of mercury on any one curve and within ± 2 or 3 mm on simultaneous curves, and time relations, to within \pm five milliseconds.

Comparison of Pulse Contours and Pressures in Different Arteries—It has been shown elsewhere^{4b} that as the pulse wave travels from the aorta out to the periphery the systolic pressure increases. The pulse wave augments and accelerates as it sweeps out, but it levels down to about the same diastolic values in all arteries. As may be seen in figure 1, this increase was noted in the pulse waves in the arm arteries in both the patient with coarctation (*IA*) and the normal control (*IB*), the respective curves do not differ essentially in contour.

In the normal subject this increase in systolic pressure is greater in the aorta and the legs, but in the patient with coarctation the lesion prevented the sweep of the pulse wave through the aorta and the usual augmentation in systolic pressure did not occur (compare curves *II A B* and *C*). The pulse pressure is much smaller below the coarctation than above, because the various collateral channels offer resistance to blood flow and have different pulse transmission times. Consequently, in pulses

5 (a) Woodbury, R. A., Robinow, M., and Hamilton, W. F. Blood Pressure Studies on Infants, *Am J Physiol* **122** 472, 1938. (b) Robinow, M., Hamilton, W. F., Woodbury, R. A., and Volpitto, P. P. Accuracy of Clinical Determinations of Blood Pressure in Children, with Values Under Normal and Abnormal Conditions, *Am J Dis Child* **58** 102 (July) 1939. Hamilton and others^{4b}

taken below the coarctation the upstroke is delayed and slow, the peak is broad, low and rounded and the contour during diastole is almost a smooth curve. There are no landmarks indicating the beginning of diastole. The pulse records taken by the direct method have contours very similar to sphygmographic tracings of the superficial pulses of patients with coarctation of the aorta.⁶

Normally the diastolic pressure and the mean pressure are about the same in the arms and in the legs. In the patient with coarctation (fig 1, *IIA*) the diastolic value was 6 mm lower in the legs than in the arms. The mean blood pressure (measured by planimetric determinations of the areas of the respective curves) was 20 mm less in the legs.

The height of the mean pressure head around the coarctation is of particular interest as an index of the resistance of the collateral circulation. Anxiety and moderate excitement raised it from 20 mm of mercury (fig 1, *IIA*) to 29 mm (fig 1, *IIB*). This suggests a vasomotor control of the collateral vessels.

Effects of Occlusion—The pulse wave sweeping out through the artery is changed in contour and height as it meets an obstruction.⁷ This is illustrated by the curves recording the pressure in the brachial artery just central to the temporary occlusion produced by digital compression. Figure 1, *III*, shows the original curves of brachial and femoral pressure before and during the occlusion. The systolic pressure increased 50 mm, and the diastolic pressure and the mean pressure went up 3 to 5 mm in the brachial artery. The femoral pressure rose less than 2 mm. Occlusion of the brachial artery thus produced little effective increase in peripheral resistance. When the femoral artery was occluded in the same manner, there was no change in contour and only a slight rise (10 mm) in the general level of blood pressure. The rise affected the brachial as well as the femoral pressure and was considered due to an effective increase in peripheral resistance.

Effects of Coughing and Straining—Coughing elevated the blood pressure in both the femoral and the brachial artery (fig 1, *IV*).^{1b} The source of this elevation of pressure is quite different from the source of the ordinary rise in systolic pressure—the heart. After a cardiac systole, the rise in pressure in the femoral artery is fifty to fifty-five milliseconds later than in the brachial artery. However, the pressure went up in the femoral artery during a cough as soon as, or sooner than, in the brachial artery. This means that the rise in arterial pressure

6 (a) Hamilton, W. F., and Abbott, M. E. Coarctation of Aorta of Adult Type, *Am Heart J* **3** 381, 1928. (b) Blumgart and others.³

7 Bazett, H. C., and Laplace, L. B. Studies on the Indirect Measurement of Blood Pressure, *Am J Physiol* **103** 48, 1933. Woodbury and others.^{5a}

EXPLANATION OF FIGURE 1

Fig 1—The following abbreviations are used for the arteries axillary, Ax, brachial, Br, radial, R, femoral, F, dorsalis pedis, D P T indicates the time interval between appearance of pulse in different arteries, M, the mean blood pressure Msec indicates milliseconds, sec, seconds The term "pulse" refers to a calibrated record of arterial pressure changes during a cardiac cycle

I A, reconstruction of curves of simultaneous pulses in axillary and radial arteries of patient with coarctation Blood pressure in mm Hg, Ax = 163/100, M = 124, R = 172/98, M = 122 T = 50 msec Time, 0.25 sec

I B, same as *I A*, normal person Ax = 110/64, M = 87, R = 118/63, M = 86 T = 49 msec Time, 0.25 second

II, reconstruction of curves of simultaneous pulses in the arm and leg Time, 0.25 sec *A*, patient with coarctation Br = 161/88, M = 113, F = 105/82, M = 93 T = 55 msec *B*, same Br = 198/110, M = 141, D P = 131/98, M = 112 T = 103 msec *C*, hypertensive patient Ax = 183/120, M = 146.5, F = 200/118, M = 146.8, D P = 236/113, M = 143 T from Ax to F = 30 msec, F to D P = 50 msec

III, simultaneous pulses from the brachial and femoral arteries of patient with coarctation Photographs of original records Occlusion of the brachial artery by digital compression, just below the needle, was started during the diastole of the second beat Br = 160/91 before occlusion and 208/94 when occluded F = 101/88 before and 103/89 during occlusion of the brachial artery Time, 1 second

IV, effect of coughing on blood pressures in the brachial and femoral arteries of patient with coarctation *A*, weak cough *B*, prolonged cough The upper curves, in continuous lines are, reconstructions of recorded curves In *A*, the broken lines show the contour of the normal pulse curve The lower groups of curves represent the excess above normal of the actual arterial pressures, i.e., the contribution of the cough to the pressure

V, effect of straining on the pulses in the brachial and femoral arteries of patient with coarctation *A*, strain commences at elevation of curve during diastole T = 50 msec *B*, just after commencement of strain, T = 45 msec *C*, 16 sec later during straining T = 80 msec *D*, just after strain ceases T = 80 msec *E*, 5 sec after *D* T = 45 msec

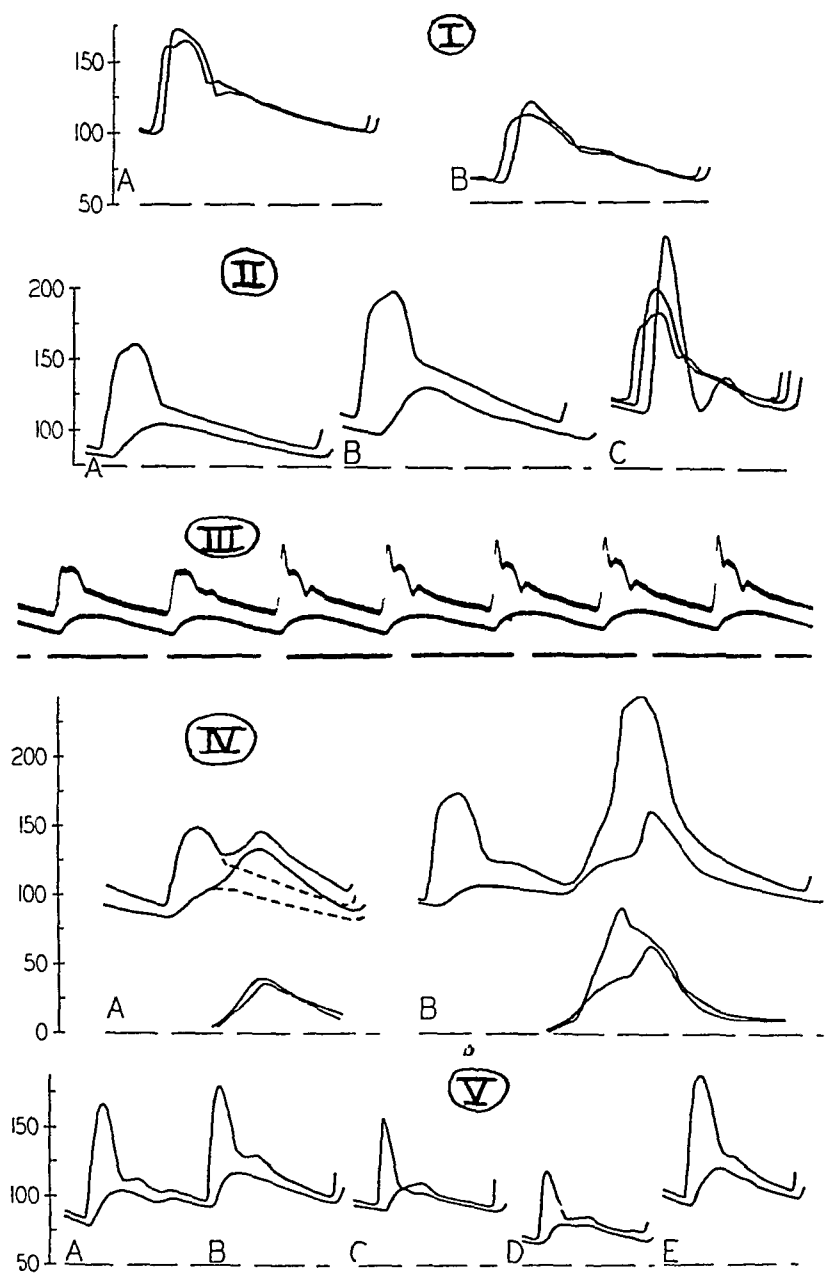


Figure 1

from coughing appeared both above and below the coarctation, without its propagation through the tortuous channels forming the collateral circulation. The rise from coughing affects simultaneously the aorta and its branches both above and below the coarctation.

When the cough was short and weak, occurring early in diastole (fig 1, *IV A*), the rise in the femoral pressure (34 mm) was as large as that in the brachial pressure (32 mm). These rises in pressure were quite different from those of cardiac origin (fig 1, *IIA, B*), in which the rise (and hence the pulse pressure) in the femoral artery is far less than that in the brachial artery.

When the cough was stronger, late in diastole and more prolonged (fig 1, *IV B*) a different picture was seen. At first (as in fig 1, *IV A*) the femoral pressure increased by the same amount as the brachial, but it failed to continue to do so. The excess pressure produced by the cough became much greater in the branches of the upper reservoir than in the arteries of the leg. However, the femoral pressure rose rapidly with the next systolic filling of the lower arterial reservoir. The elevations of the blood pressure in the femoral and brachial arteries as a result of the cough again became about equal and remained equal as the cough ceased.

The architecture of the diaphragm indicates that the pressure in the abdomen on the lower part of the aorta is just as great as or greater than the pressure in the thorax acting on the upper part of the aorta. Why, then, should coughing cause less rise in blood pressure in the branches of the lower aorta than in those of the upper aorta?

The only explanation that we offer is based on the supposition that the lower reservoir, with its large drainage, becomes depleted before the cough is over, while the upper reservoir, with its smaller drainage does not become depleted so rapidly. The drainage from the upper reservoir is restricted not only because of the smaller size of the arms as compared with the legs but also because the cough has raised the pressure in the abdomen and the cranial cavity^{4b} so as to equal that in the thorax, thus preventing any increase in blood flow to these parts.

When systole occurs, the pressure head around the coarctation is increased, the lower reservoir is replenished and the excess pressure produced by coughing becomes approximately equal in the arteries of the arm and leg.

As shown in figure 1, *V*, straining caused the characteristic four phase arterial pressure changes^{4b}. At first the pulse contours were not appreciably changed and the increases in systolic and diastolic pressure in the femoral and brachial arteries were the same, 12 mm systolic and 13 mm diastolic, indicating that the effects of the strain appeared simultaneously above and below the coarctation. The increases were not propagated

through the tortuous collateral channels but originated from an elevated intrathoracic and intra-abdominal pressure

In the second phase (fig 1, *VC*) the pulmonary reservoir became partly depleted. Cardiac filling was inadequate, and the pulsations were somewhat of the empty type, with a lowered pulse pressure. However, they were not mere ripples on the arterial tree, as in the normal person. This is due to the fact that the straining done by this patient was ineffective, elevating the systolic pressure less than 15 mm, as compared with elevations of 35 to 57 mm reported for the normal person^{4b}. Although the patient was well and muscular, he seemed unable to exert himself effectively.

In the third phase (fig 1, *VD*), when the patient ceased to strain, the pressures fell to the level of the effective intrathoracic and intra-abdominal blood pressures, which had ceased to augment the blood pressure.

In the fourth phase (fig 1, *VE*), with the reduction of the intra-thoracic abdominal pressure the heart became better filled. The systolic and diastolic pressures increased, the pulse pressure widened and the dicrotic notch was higher on the diastolic curve, showing that the arteries were better filled.

Pharmacologic Studies—Figure 2, *I*, shows the effects of the intravenous injection of epinephrine hydrochloride (0.1 mg) on pressure contours recorded simultaneously for the radial and the dorsalis pedis artery. Figure 2, *IA*, shows the curve taken just before the injection. The next curve shows the increase in pressure in both arteries eighteen seconds after the injection, evidently the drug had stimulated the heart to greater activity but had not yet caused appreciable constriction of the channels around the coarctation.

Twenty-seven seconds after the injection (fig 2, *IC*) the radial pressures increased still further, but the pressures below the coarctation actually became lower. The collateral channels had evidently constricted, and the rate of descent of pressure during diastole was increased in both curves. At the same pressures the time required for equal falls in pressure had decreased 15 per cent in the radial artery and 30 per cent in the dorsalis pedis artery. This decrease and the very high peak of systolic pressure in the radial artery probably mean that the distensibility of the great vessels had become less through the action of the drug. It could be interpreted as indicating that the drainage of blood through the arterioles had become greater, but the fact that the cardiac output is diminished shortly after injection of epinephrine⁸ and the known action of the drug on arterioles do not render this suggestion

8 Hamilton, W. F. Some Mechanisms Involved in the Regulation of the Circulation, *Am J Physiol* **102**: 551, 1932.

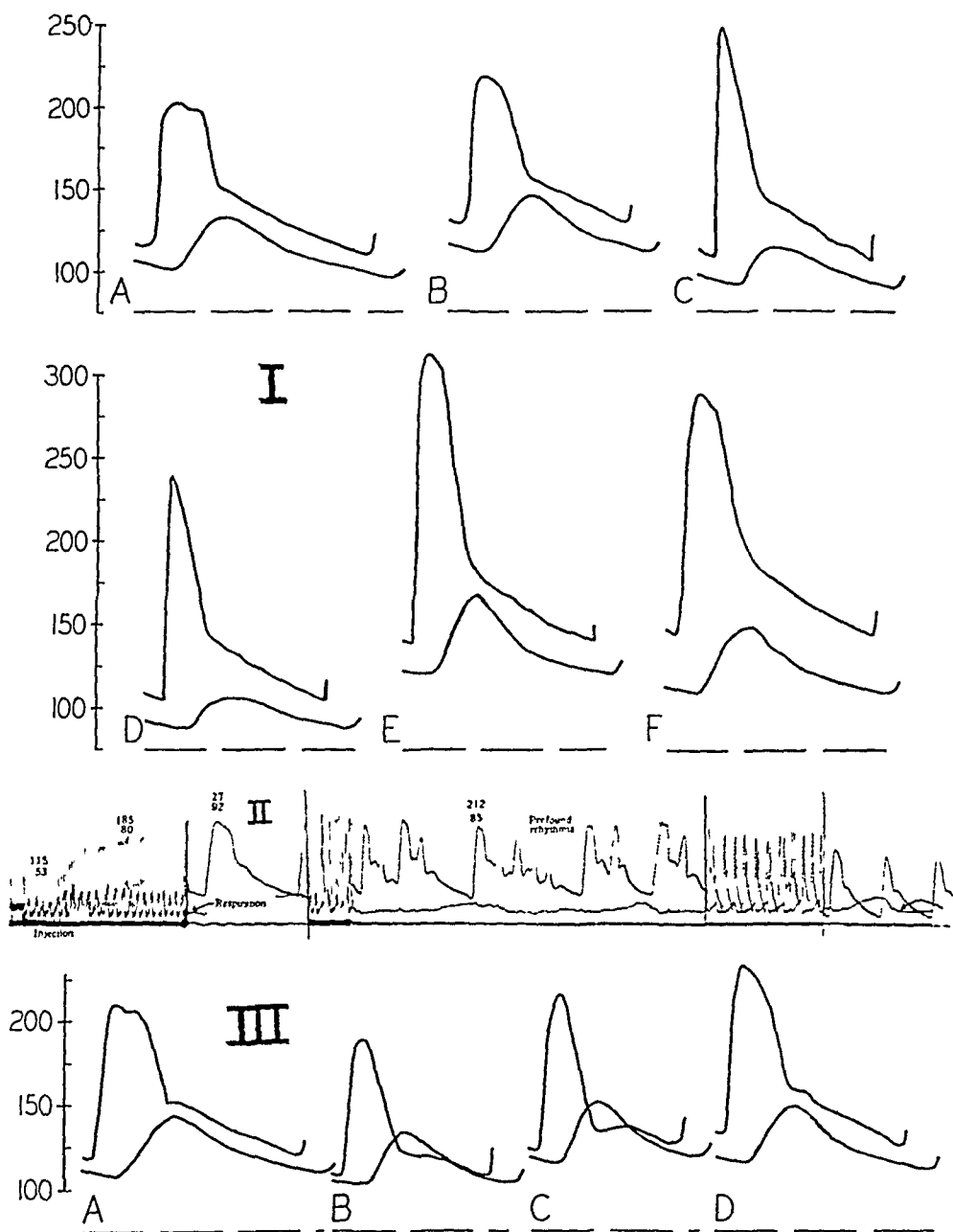


Fig 2—The abbreviations in this legend are explained in figure 1 I, effects of 0.1 mg epinephrine hydrochloride injected intravenously on simultaneous pulses in the radial and dorsalis pedis arteries of a patient with coarctation Time, 0.25 sec A, before injection R=203/111, M=146, D P=133/98, M=113, T=88 msec B, 18 sec after injection R=221/132, M=165, D P=147/114, M=129, T=75 msec C, 27 sec after injection R=251/110, M=151, D P=117/95, M=106, T=80 msec D, 33 sec after injection R=238/105, M=143, D P=106/88, M=97, T=85 msec E, 60 sec after injection R=312/140, M=192, D P=167/121, M=138, T=82 msec F, 90 sec after injection R=287/144, M=193, D P=148/109, M=125, T=83 msec

II, effects of epinephrine in patients with asthma These original curves show the brachial blood pressure, the respiratory rate and the time in 1 second intervals At the point marked "injection" 0.2 mg of epinephrine hydrochloride was injected intravenously Note the very high blood pressure and the profound arrhythmia The rate of recording was changed so that some of the cardiac cycles are spread out more than others

III, effects of 1 pearl of amyl nitrite on the radial and dorsalis pedis pulses in patient with coarctation A, before effect of drugs R=209/121, M=155, D P=143/110, M=124, T=95 msec B, 40 sec after inhalation started R=188/108, M=133, D P=133/105, M=117, T=85 msec C, 53 sec after inhalation started R=217/128, M=152, D P=152/120, M=133, T=78 msec D, 90 sec after inhalation was discontinued R=234/126, M=163, D P=150/112, M=129, T=89 msec

likely. In the dorsalis pedis artery the increased rate of descent of pressure during diastole is probably contributed to by the lessened diastolic inflow from the collateral circulation.

Sixty and ninety seconds after injection, the main changes seemed to be those due to the building up of the cardiac output, which is known to be a secondary effect of epinephrine.⁸ The pressures in both arteries increased, and the gradient of pressure across the coarctation became higher.

These effects of the injection of epinephrine bring out the limitations of the vascular systems of patients with coarctation of the aorta and explain why emotional upsets are especially dangerous to them. In such patients vascular accidents in the upper arterial reservoir and the rupture or decompensation of the heart are bound to be far more frequent¹ than in the normal person.

A slightly larger dose (0.2 mg.) of epinephrine hydrochloride was given intravenously to a 22 year old patient with asthma. The brachial blood pressure increased from 115 to 227 systolic and from 53 to 92 diastolic, and profound arrhythmia occurred (fig 2, II). This demonstrates a further toxic effect of epinephrine, that of increasing the irritability of the heart. More emphasis should be placed on the fact that intravenous injections of a 1:1,000 solution of epinephrine hydrochloride are dangerous, even to patients with circulatory collapse.

Inhalation of amyl nitrite produced effects opposite to those of epinephrine (fig 2, III). The effects appeared more slowly because the drug (3 minims, 0.19 cc.) was inhaled over a period of fifty-five seconds. As the drug began to take effect, the radial peak became narrower and lower, the diastolic pressure less and the diastolic slope flatter, the mean blood pressure decreased 22 mm., and the pulse rate increased. Below the coarctation the rise in systolic pressure was steeper and nearly as great as before the drug was given, the mean pressure was lowered only 7 mm. The resistance of the collateral system had been much reduced by the drug. As is evident, the mean pressure head was lower, and the pressures for both the radial and the dorsalis pedis artery were at similar heights during diastole. The fact that the systolic pressure in the dorsalis pedis artery exceeded that in the radial artery is robbed of much of its apparent meaning by the difference in timing of the two curves.

Fifty-three seconds after inhalation began (fig 2, III C) there was evidence that the collateral system was widely open. The pulse wave was transmitted more quickly across the coarctation. The mean pressure of the upper vessels was not yet back to normal, but that in the lower vessels was well above normal and the mean gradient between the two was still low. Ninety seconds after discontinuing the inhalation of the

drug, the patient was reacting against its vasomotor action by increased cardiac output⁸. The pulse curve for the radial artery gave every indication of a very large stroke volume. The mean pressure below the coarctation was still above normal, notwithstanding the fact that the gradient of the pressure causing flow around the coarctation was again above normal.

It should be pointed out that the reaction to amyl nitrite carries a danger that is particularly marked in this type of patient. The compensatory increase in cardiac output does not in most persons cause the rise in blood pressure seen in this patient whose peripheral outflow was so badly restricted.

The type of pulse which occurs during the period of low pressure is that usually found in the normal person under such conditions. This type of pulse contour would produce the classic superficial pulse forms⁹ observed after inhalation of amyl nitrite.

SUMMARY

Direct optical blood pressure tracings were made simultaneously from various arteries of a patient with coarctation of the aorta. Within arteries above the coarctation the systolic pressure was 160 mm. of mercury and the diastolic 88 (mean 113), below the coarctation the pressure was 105 systolic and 82 diastolic (mean 93). Pulse contours recorded from arteries above the coarctation were of normal appearance, from arteries below the coarctation they were flat, smooth and somewhat delayed. This is the opposite of the variation in contour that occurs normally.

Simultaneous rises in pressure produced in the lower and upper arteries by coughing and straining are discussed in detail.

After injection of epinephrine hydrochloride the pressure rose in the upper arteries, and rose and then fell in the lower arteries. Later it rose in both systems. The records indicate that there was an increase in the resistance of the collateral circulation and peripheral arterioles and an increase in the elasticity of the larger vessels.

Inhalation of amyl nitrite produced changes which were generally the reverse of those produced by epinephrine.

Prof. J. H. Sherman and Dr. M. B. Hatcher, of the department of surgery, helped to expose the arteries for puncture. Dr. B. D. Bosworth, formerly of the department of medicine, helped to take the records.

⁹ Sollmann, T. A. *Manual of Pharmacology*, ed. 5, Philadelphia, W. B. Saunders Company, 1936, p. 480.

STUDIES IN DYSTROPHIA MYOTONICA

II CLINICAL FEATURES AND TREATMENT

JAMES J. WARING, M.D.

ABE RAVIN, M.D.

AND

CHARLES E. WALKER, JR., M.D.

DENVER

Dystrophia myotonica suffers from an obscurity undeserved because, contrary to general impression, the disease is fairly common, frequently unrecognized and of great general medical interest. Of the 13 patients included in this report, 8 were discovered by the purposeful investigation which we made of the families of our patients previously recognized to have the disease. Of the first group of 5 patients presenting themselves at the Colorado General Hospital for treatment, not one heretofore had had his condition correctly diagnosed. All 13 patients came under our observation between 1935 and 1938. Fleischer's¹ report in 1918, pointing out the hereditary features of the disease, was based on a study of 38 patients seen in the ophthalmic clinic at Tübingen, Germany. Maas² in 1937, from the National Hospital for Nervous Diseases in London, published his investigation of 57 families, among which he found 127 unmistakable cases of the disease and 205 suspected cases. Kennedy and Wolf^{3a} in 1937 recorded their observations on the effects of treatment with quinine in 18 cases of dystrophia myotonica. In 1938 Kolb, Harvey and Whitehill^{3b} added 8 cases to the rapidly mounting number of recently recorded cases. It is evident that the disease is not rare and that the degenerative changes are so widespread that ophthalmologist, neurologist or internist may be called on to diagnose and to treat the disease.

From the Departments of Medicine and Ophthalmology, University of Colorado School of Medicine and Hospitals.

1. Fleischer, B. Ueber myotonische Dystrophie mit Katarakt. Eine hereditäre, familiäre Degeneration, *Arch f. Ophth.* **96** 91, 1918.

2. Maas, O. Observations on Dystrophia Myotonica, *Brain* **60** 498, 1937.

3. (a) Kennedy, F., and Wolf, A. Quinine in Myotonia and Prostigmia in Myasthenia. A Clinical Evaluation, *J. A. M. A.* **110** 198 (Jan 15) 1938. (b) Kolb, L. C., Harvey, A. M., and Whitehill, M. R. A Clinical Study of Myotonic Dystrophy and Myotonia Congenita with Special Reference to the Therapeutic Effect of Quinine, *Bull. Johns Hopkins Hosp.* **62** 188, 1938. (c) Wolf, A. Quinine. An Effective Form of Treatment for Myotonia, Preliminary Report of Four Cases, *Arch. Neurol. & Psychiat.* **36** 382 (Aug) 1936.

Patients afflicted with myotonia congenita, or Thomsen's disease, manifest a peculiar difficulty in relaxing muscles which have been contracted. This muscular difficulty is known as myotonia. In Thomsen's disease, most of the skeletal muscles show myotonia and are hypertrophied. For many years patients with myotonia and atrophy of certain muscles, instead of hypertrophy, were thought to have an atypical form of myotonia congenita. In 1909 Batten and Gibb⁴ and Steinert⁵ independently noted that in these instances the myotonia was limited in distribution and that the muscle atrophy showed a characteristic pattern. The myotonia, they pointed out, was limited mainly to the hand grasp but did at times affect the muscles of mastication and the muscles of the lower extremities. The muscular atrophy involved especially the facial muscles, the sternocleidomastoids, the muscles of the forearm, the extensors of the legs and the dorsiflexors of the feet. In 1912 Curschmann,⁶ in emphasizing the importance of the extra-muscular dystrophic signs, cataract, baldness, testicular atrophy and various endocrine changes, called attention to the highly characteristic symptom complex of dystrophia myotonica.

Essential details of the case histories of 13 patients with dystrophia myotonica follow.

REPORT OF CASES

CASE 1—Myotonia, atrophy, cataracts, baldness, probable testicular atrophy, basal metabolic rate — 37 per cent

O. M., a 43 year old man, first came to the clinic in December 1935, complaining of poor vision. His oldest sister, N. M., is described in case 2, another sister, J. L., in case 3, a brother, C. M., in case 4, and a nephew, H. M., in case 5 (fig. 1). His father was operated on for cataract at about 60 years of age, a sister of his father was operated on for cataract at 65 years of age, a half-sister of his mother was thought to have had "locomotor ataxia," because of a progressive inability to use her lower extremities from about the age of 30 years to her death at 64 years.

The patient was born in Illinois in 1895. He finished the eighth grade at the age of 16 years. He has been a farmer and worked as a carpenter. He enlisted in the army in 1917 and was discharged in 1919. He had measles, mumps and whooping cough in childhood and pneumonia and pleurisy in 1930. He was married in 1924 and has no children.

The patient has worn glasses since 12 years of age. At the age of 30 he was told that he had incipient cataracts. A few years later his vision began to fail rapidly, and at 40 years of age he was almost blind. Examination at that time revealed almost mature cataracts of both eyes. Slit lamp examination showed an almost complete opacity of each lens, with highly refractile globular opacities, which cast bluish reflections. In January 1936 a cataract was removed.

4 Batten, F. E., and Gibb, H. P. Myotonia Atrophica, *Brain* **32** 187, 1909.

5 Steinert, H. Ueber das klinische und anatomische Bild des Muskelschwundes der Myotoniker, *Deutsche Ztschr. f. Nervenhe.* **37** 38, 1909.

6 Curschmann, H. Ueber familiäre atrophische Myotomie, *Deutsche Ztschr. f. Nervenhe.* **45** 161, 1912.

from the left eye, and in February 1936, from the right eye. At present his vision with glasses is 20/20. For many years he has had some irritation of his eyelids and a slight discharge from his eyes.

In 1922, at the age of 27, he noticed that he had a poor grip, and in 1928 he noticed that if he grasped an object he could not immediately release it. The weakness of his hand grasp has gradually increased, the stiffness has not changed very much. During the last four to five years, on beginning movement after rest the muscles of the lower extremities have felt stiff. The stiffness in his hands and legs is worse in cold weather. He says that when he works his hands seem to be strong, but after resting several days they seem to lose strength.

For the last twelve to fourteen years the patient has been very intolerant to cold, and his hands and feet get cold very easily. During the same time he has lost both strength and energy. In October 1933 he was found to have a basal metabolic

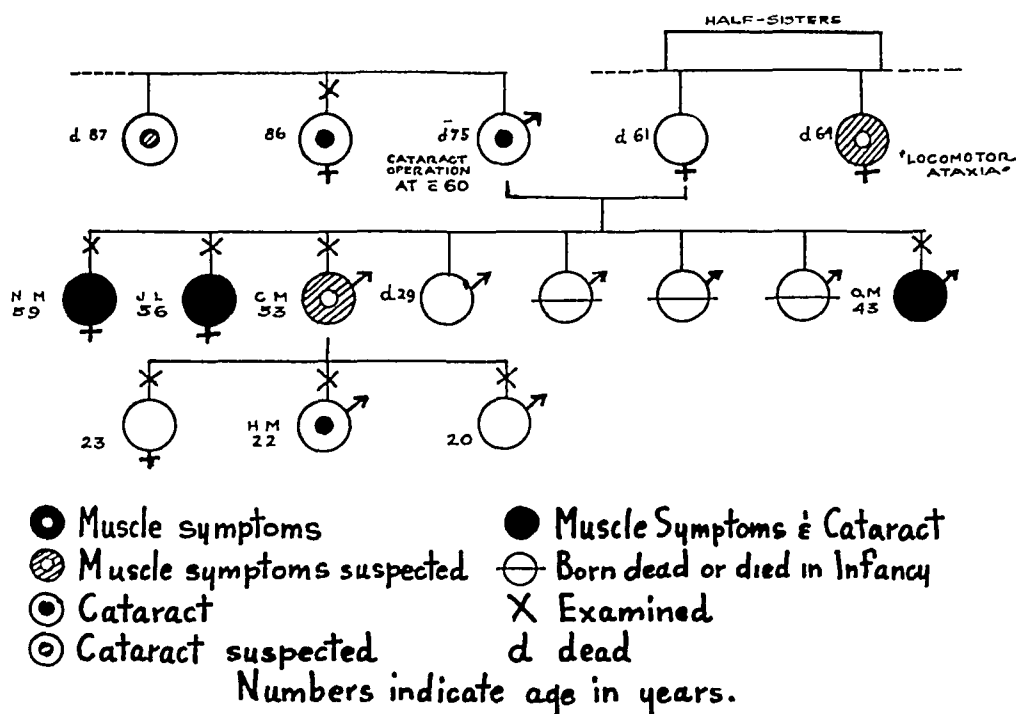


Fig 1—Family M (cases 1, 2, 3, 4 and 5)

rate of —37 per cent. Thyroid was administered, and the basal metabolic rate increased to normal with a dose of 10 grains (0.65 Gm) one day alternated with 5 grains (0.32 Gm) the next day. With this treatment the patient's sluggishness and malaise were improved. When seen in December 1935 the patient was still taking thyroid but did not think he was greatly benefited. He felt that there had been no change in the stiffness of his hands. During the last two years in which we have seen him he has not been taking thyroid, and he has noticed little if any difference in his condition.

Physical examination in January 1938 revealed a well nourished, rather tall, fairly well developed white man of 43 years of age, with an expressionless "hatchet facies." He talks rather slowly. The gait is slightly but definitely of the steppage type, with some "slapping." No blepharitis is evident at present. The lens in each eye has been removed. The thyroid is easily palpable and enlarged about one and a half times. The left lobe is somewhat larger than the right.

and is firmer than normal, but not markedly so (The patient believes that his thyroid has been enlarging during the last year) The lungs and abdomen are normal The testicles are somewhat smaller and softer than normal

In the examination of the cardiovascular system, a roentgenogram revealed structures of the heart and aorta to be of normal size and shape The heart sounds were faint The blood pressure was 100 systolic and 68 diastolic, and the pulse rate was 56 per minute The peripheral vessels showed little if any evidence of sclerosis An electrocardiogram made on Feb 24, 1938 showed a low voltage of all P waves (the highest being less than 1 mm), a PR interval of 0.24 second, low voltage of the QRS waves (the largest excursions being 5 mm in lead II) and normal T waves (the voltage in lead II being 3.5 mm)

Examination of the neuromuscular system revealed that the patient has the typical myopathic facies, as a result of atrophy and weakness of the muscles of expression The temporal muscles are moderately atrophied, but the masseters appear in good condition The sternocleidomastoid muscles are markedly atrophied The muscles of the forearm are moderately atrophied The hand grasp is weak, more so on the right, although the patient is right handed The extensor muscles of the forearm appear more affected than the flexors Flexion of the thigh and leg is somewhat weakened Dorsiflexion of the feet is weak, but definite atrophy of the dorsiflexors is questionable Active myotonia is present to a marked degree in the hand grasp and to a much less degree in the movements of the toes and ankles The mechanical irritability of the muscles is increased, and mechanical myotonia is evident in the muscles of the chin, the extensors of the wrist and fingers, the tongue, the deltoids and the muscles of the thenar and hypothenar eminences Electrical myotonia is evident in the muscles of the thenar and hypothenar eminences The biceps, abdominal, patellar and achilles tendon reflexes are present The Babinski reflex and the Romberg sign are normal

The Wassermann test and the Eagle flocculation test gave normal results Examinations of the urine gave normal results The blood counts showed no persisting abnormality A roentgenogram of the skull in January 1936 showed a normal sella turcica and a pineal body, partially calcified, in normal position The basal metabolic rate on Oct 15, 1933 was -37 per cent and the value of cholesterol in the blood at the same time was 180 mg per hundred cubic centimeters While the patient was taking thyroid, the basal metabolic rates varied from -26 to $+8$ per cent In December 1935 three determinations were made of the calcium content of the blood, showing 11.0, 10.1 and 11.2 mg per hundred cubic centimeters, the associated phosphorus values were 3.8, 3.8 and 3.3 mg per hundred cubic centimeters

The results of roentgenologic examination of the gastrointestinal tract on Feb 18, 1938 were reported as follows Barium sulfate passed down the esophagus in a normal manner, the stomach appeared of normal size, shape and position, the pylorus seemed to function in a normal manner, definite roentgen evidence of an organic lesion in the duodenum was lacking, the appendix and the gall-bladder were not clearly visualized, there was a slight ptosis of the transverse colon, there were spasticity and stasis in the colon, with lack of haustrations in the descending colon and the sigmoid flexures

7 When the muscle was stimulated to contract by mechanical or electrical means, we have referred to the "mechanical irritability" or the "electrical irritability" of the muscle and have employed the terms "mechanical myotonia" and "electrical myotonia" When the muscular contraction was voluntary, we have employed the term "active or voluntary myotonia"

CASE 2—*Myotonia, atrophy, cataracts, basal metabolic rate —31 per cent*

N M, a 59 year old white woman, a sister of O M (case 1) came to the clinic in July 1937 and gave as her chief complaint a difficulty in walking, which had been present for about one and a half years and appeared to be due to loss of strength in the left lower extremity. When examined in January 1936 she did not complain of this difficulty in walking, although at the time a weakness of the left quadriceps was observed. She is inclined to stumble and fall and has marked difficulty in going up steps. During the last seven years she has at times had difficulty with stiffness in her fingers. When she tries to shovel coal, her hands cramp and she is unable to open them. When her hands are cold or when she is nervous, this stiffness is worse. The hand grasp has become progressively weaker. During the last four to five years she has noticed that at times, when she yawns deeply, her jaw is stiff and she seems temporarily unable to close it. She believes that it may be due to a slight forward displacement of the jaw. Although she never had very much energy and has always tired easily, this condition has become worse in the last six years.

Ever since the age of 22 years, the patient has had red eyelids and sore eyes. At 27 years of age she was fitted with glasses. When she was 46 years of age, ring opacities were found in each lens and small specks of opacity throughout the lens. Her vision with glasses was 20/40 in the right eye and 20/25 in the left eye. Vision has gradually failed but is not as yet very poor.

For the last twenty years or more, the patient has had "stomach trouble," consisting mainly of distention and flatus. The distention begins shortly after eating and lasts a few hours.

She was born in 1879 in Illinois and went through the fourth grade in school. She had whooping cough and mumps in childhood, measles at 22 years of age and smallpox at 28 years. She had pneumonia in 1917 and again several years later. Her menstrual periods began at the age of 12 years and were markedly irregular, usually late, at two, three or four month intervals. The flow was scanty. The menopause occurred at 42 years. She married at 26 years and has never been pregnant.

A physical examination of the patient in September 1937 revealed a fairly tall, well proportioned and well nourished white woman of 59 years, who appeared to react somewhat more slowly than normally. She is not very intelligent but very cooperative. The voice is normal. The abnormal gait appears to be due to some foot drop associated with a difficulty in lifting the left leg. The skin is somewhat dry, and the hair is coarse and dry. Her hands and feet are cyanotic and cold. The left lobe and the isthmus of the thyroid are slightly enlarged, probably because of the presence of a nodule in that region. The lungs and the abdomen are normal.

A chronic blepharitis was observed to be present in each eye. The cornea, the anterior chamber and the iris of each eye are normal. Slit lamp examination showed incipient cataracts, particularly subcapsular and cortical, with typical punctate opacities, some of which had become confluent, under the anterior and posterior capsules. Bluish refractile bodies, occasionally appearing yellow or green, are present in both lenses. The remainder of the media and the fundi show no particular abnormality. The vision is 20/50 in each eye, improved to 20/25 with proper glasses.

In a roentgenogram (September 1937) the heart and the aorta appeared to be of normal size and shape. The blood pressure was 138 systolic and 90 diastolic. The heart sounds were slightly muffled at the apex. Both the first and the second sound

seemed prolonged. The pulmonic second sound was greater than the aortic. The electrocardiogram (September 1937) showed a PR interval of 0.20 second and a left axis deviation, the T waves were normal.

The muscles of expression and the temporal and masseter muscles were somewhat weakened and atrophic. The sternocleidomastoid muscles were markedly atrophic. The triceps and the extensors of the wrist and fingers were weak, but definite atrophy was lacking. The flexors of the thigh were possibly weakened, and the extensors of the thigh and the flexors of the leg were definitely weakened. Dorsiflexion of both feet was weak, and, especially on the left, the dorsiflexor muscles were somewhat atrophied. Mechanical irritability was of normal degree. Mechanical myotonia was observed in the extensors of the hands and fingers, the thenar and hypothenar eminences and the tongue. Electrical myotonia was obtained with strong currents in the thenar and hypothenar eminences. The biceps, triceps and patellar reflexes were present. The achilles tendon reflexes were not obtained. The Chvostek and the Trousseau sign were absent.

The results of the Wassermann and the Eagle flocculation test were negative. The basal metabolic rate in January 1936 was —31 per cent. In January 1936 the calcium and the phosphorus content of the blood were respectively 12.2 and 3.6 mg per hundred cubic centimeters, the cholesterol content was 148 mg. In September 1937 the calcium and the phosphorus content were 10.0 mg and 4.6 mg per hundred cubic centimeters, the cholesterol content was 180 mg, and the plasma chloride content (as sodium chloride) was 658 mg.

Roentgen examination of the gastrointestinal tract in December 1938 showed slight transient cardiospasm, the stomach appeared to be of normal shape, size and position, a slight inconstant defect was noted in the first portion of the duodenum, there was no unusual patency of the pylorus, there was a slight six hour gastroduodenal residue, the appendix and the gallbladder were not visualized, there was a slight ptosis in the transverse colon.

CASE 3—*Myotonia, atrophy, cataracts*

J. L., a 56 year old woman, a sister of O. M. (case 1) and N. M. (case 2), was examined in November 1937, in the course of investigations of relatives of our original patients (fig. 1). She complained of attacks of weakness, occurring at intervals of a few weeks to several years for over thirty years. During these attacks she feels faint and weak but she has never lost consciousness and recovers when she lies down for a short time. She has been tiring easily in the last ten years. During the last eight to ten years she has had difficulty in relaxing her hand grasp, especially on exerting a stronger effort, such as pulling weeds. This difficulty is of about the same severity as when it was first noticed. The strength of the hand grasp the patient believes unchanged. During the last few months she has had a soreness in the left thigh, and it has been difficult for her to walk up steps because of an inability to bring the weight up on the left leg. The legs have not been stiff. The hands became cold easily, but there is no special sensitivity to cold.

The patient has worn glasses since the age of 16 years. When she was 52 years old, incipient cataracts were found. She cannot see very well at present. Her eyes are red most of the time and in the morning have "matter" in them.

She had measles and whooping cough in childhood, malaria at 10 years of age, severe mumps at 18 and "walking typhoid" at 20. She was born in Flora, Ill. She did not finish high school. Her menstrual periods started when she was 15 years of age and were never regular. The menopause occurred when she was 43 years of age. She is married and has never been pregnant.

Physical examination in November 1937 revealed a rather tall, well proportioned and well nourished white woman of 56 years. The skin is a pale waxy color which gives her the appearance of being chronically ill. She is alert, fairly intelligent and cooperative. She walks and talks without noticeable difficulty. The thyroid is not enlarged, although the right lobe seems more palpable and more firm than the left. The lungs are normal on percussion and auscultation. The heart is not enlarged on percussion, and the sounds are normal in character. The blood pressure is 122 systolic and 80 diastolic and the pulse about 80. There is no evidence of peripheral sclerosis.

The eyes were examined in May 1938 by Dr. Perry E. Duncan, of Taylorsville, Ill., who supplied the following report: "The defect in the lens in each eye is slightly more pronounced than it was on my former examination, in January 1934. The right lens shows a peripheral spoke at 6 o'clock, extending to a point midway between the central and the peripheral portion of the lens. This clouding has the appearance of that usually found in an incipient cataract. The anterior portion of the capsule of the lens shows minute sclerotic areas, which are of sufficient density to account for the impairment of vision. Examination of the left lens shows a peripheral area of clouding, located at 7 o'clock. The density and width of this cataractous area are slightly more pronounced than those of the right lens. The areas of sclerosis on the anterior capsule were more numerous on the lower half of the anterior capsule."

The vision with glasses at that time was 20/32 — 1 in the right eye and 20/40 — 1 in the left eye. Reexamination of the eyes in November 1938 showed the condition very much as just described, except that the opacity of the left lens had increased until a vision of 20/800 was all that remained. A chronic blepharitis was present.

In an examination of the neuromuscular system in November 1937 a slight ironing out of the facial features appeared to be present and was most noticeable around the mouth. The muscles of the forearm and hand showed no wasting, but the hand grasp on the right was definitely less than on the left and was weaker than normal. Flexion and extension of the right wrist were also weaker than those of the left. Flexion and extension of the left thigh were weaker than on the right and probably weaker than normal. Dorsiflexion of the feet was normal. A definite difficulty and slowness in opening the fist after it had been closed tightly were evident, but the difficulty disappeared after the movement had been repeated four or five times. Mechanical myotonia was present in the tongue, the extensors of the wrist, the thenar and hypothenar eminences and possibly the flexors of the wrist. Electrical examination of the muscles was not made. The biceps and patellar reflexes were present. A Chvostek sign was not present.

CASE 4—*Myotonia*

C. M., a 53 year old white man, a brother of O. M. (case 1), N. M. (case 2) and E. L. (case 3), was seen in the course of our investigations (fig. 1). During the last few years this man has noticed that when he works with a hammer or saw his hand clamps around the tool and he often has to use the other hand to get it loose. He says that his "leaders feel tight." The "cramps" vary in intensity and last from several seconds to a half-minute. They are not associated with any pain and occur in both hands but are more noticeable in the right hand, because he uses that hand most. They are worse in the cold. He has no other complaints.

Physical examination in November 1937 revealed that the patient was a well developed and well nourished 53 year old white man, who appeared to be in good

health At the time of the examination active myotonia was not elicited No definite mechanical myotonia could be determined The general muscle strength was good, and there was no atrophy Slit lamp examination of the eyes revealed no signs of cataract The heart was normal in size on percussion The heart sounds were rather faint but otherwise appeared normal Extra systoles were frequent The blood pressure was 130 systolic and 82 diastolic Electrical examination of the muscles was not made

CASE 5—*Cataracts*

H M, the 22 year old son of C M (case 4), has had trouble with his eyes for over ten years He has changed glasses repeatedly, and cannot see well at present He has been told that he has a marked myopia, and two years ago was told that he had "spots in his eyes" There are no other complaints

Examination in November 1937 revealed an alert, intelligent, ambitious young man No voluntary myotonia was evident, and the muscles appeared to be of normal bulk and strength Mechanical irritability was definitely increased, and percussion of the thenar eminences produced muscle contractions persisting only two to three seconds and therefore of questionable significance The heart was normal in size, and the sounds were normal in character The blood pressure was 108 systolic and 68 diastolic The testicles appeared normal

The examination of the eyes, which was performed in November 1937 by Dr E B Alvis, of St Louis, showed a myopia of about 4 diopters of each eye and many small bright white dots of variable size in each lens On the right side these were numerous and had a tendency to collect at the border of the adult nucleus Others, however, scattered throughout the lens substance, appeared to be more numerous in the periphery than in the center The left lens had fewer spots, and they were distributed irregularly throughout the lens

CASE 6—*Myotonia, atrophy, cataracts, baldness, testicular atrophy, basal metabolic rate — 19 per cent*

J B, 60 years old, a brother of M W B (case 7) and the father of R B (case 8) and M J B (case 9) (fig 2), stated that he was very well until thirteen years ago, when, during a game of tennis, he noticed a weakness of the right hand The patient has a peculiar mental attitude In spite of marked objective evidence of muscular weakness, he denies ever having been conscious of the weakness His first reaction is to deny everything and then to admit only the possibility of the presence of any defect It is therefore probable that the weakness has been present for more than thirteen years The weakness of the right hand has gradually progressed, and atrophy of the muscles of the forearms has become evident About seven years ago he noticed the atrophy in his left forearm About two years ago some one asked him how long his legs had been stiff This, the patient insists, is the first time he realized that anything was wrong with his legs Since that time his legs have become increasingly stiff and weak The stiffness is worse after he has been sitting for some time and in cold weather It is diminished after walking He stubs his toes when he walks His articulation has been poor for three to four years

For several years the patient has had a marked generalized weakness His hands get cold easily He has lost about 5 pounds (2.5 Kg) in the last year, and now weighs about 100 pounds (45 Kg) His best weight was 134 pounds (60.8 Kg) at the age of 20 years

He has been wearing glasses for more than fifteen years During the last five years, his eyes have been watering, and two years ago he was told that his tear ducts were "stopped up" Vision now is not very good

He had measles and whooping cough in childhood, a febrile disease ("typhoid-malaria") at 19 years and influenza at 41 and 44 years of age. He was born in Texas, one of twins. The twin brother died at 8 months of age. He went to high school but did not graduate. He has done clerical work and sold insurance. He married in 1909 and has a son (R B, case 8) and a daughter (M J B, case 9). Sexual desire and power were good in his youth and, according to the patient, are still present and unchanged.

On physical examination in September 1937 the patient appeared somewhat older than his stated age of 58 years. He is of medium height and of rather slight build, cooperative and intelligent, but he presents the peculiar mental attitude previously described. He talks in a nasal, monotonous, low-pitched voice, at times difficult to understand. He walks with a definite steppage gait, with the body flexed forward. The skin over the face is tight, thin and shiny. He is bald, and his teeth have been extracted. On examination the thyroid was not enlarged, the lungs and abdomen were normal, and the testicles were definitely smaller and softer than normal.

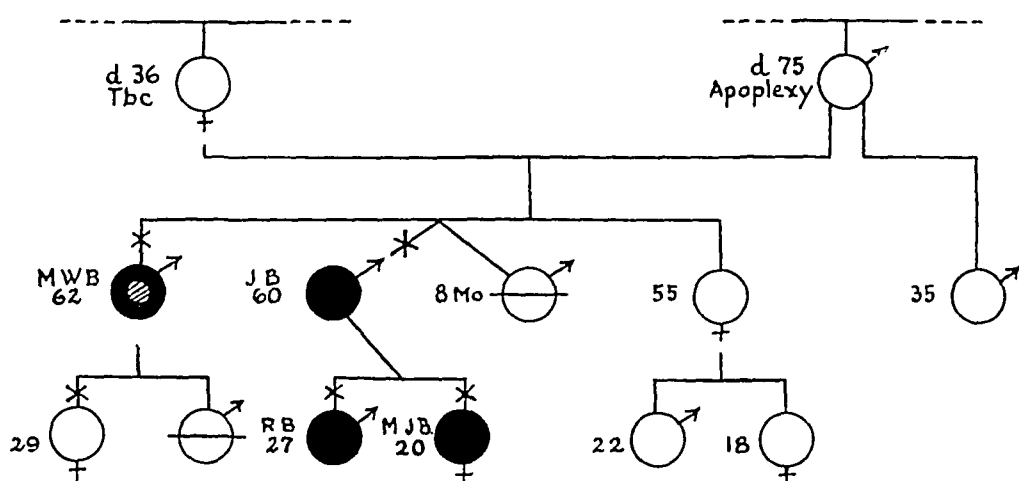


Fig. 2—Family B (cases 6, 7, 8 and 9). The legend is the same as for figure 1.

Examination of his eyes showed a chronic conjunctivitis. The cornea, anterior chamber and iris of each eye were normal. The lens in each eye showed early sub-capsular and posterior starlike opacities. Numerous small punctate opacities of various sizes occurred throughout the entire lens but were more numerous under the anterior and posterior capsules. With a slightly minus lens, the vision was normal.

The heart and the aorta were of normal size and shape as observed in the roentgenogram. At the apex, the first sound was of moderate intensity and was followed by a rather rough, fairly loud, high-pitched systolic murmur. The first sound was faint at the base. The second sounds were of moderate intensity at the apex and base. There was little evidence of peripheral sclerosis. The blood pressure was 104 systolic and 70 diastolic. The electrocardiogram was normal.

On examination of the neuromuscular system, the temporal muscles were markedly atrophic, the masseters, less so. The periorbital muscles, the muscles of the cheeks and the orbicularis oris were weak and atrophic, the typical myopathic facies being produced. Only a few fibers of the sternocleidomastoids were left. All the muscles of the shoulder girdle and of the trunk showed moderate atrophy. The triceps, the biceps and the muscles of the forearms and hands on each side were markedly atrophied. Flexion and extension of the thigh were fairly good. Flexion and extension of the legs were weak. Dorsiflexion of the feet was very

weak All the muscles of the lower extremities were somewhat atrophic Voluntary myotonia was present in the adductors of the thumbs All the muscles showed a somewhat increased mechanical irritability Mechanical myotonia was present in the chin muscles, the tongue, the deltoids, the extensors of the fingers and wrists, the thenar and hypothenar muscles, the glutei and the calf muscles Electrical testing revealed a myotonic reaction, modified by the atrophy The patellar reflexes were present The achilles tendon reflex could not be obtained Chvostek's and Trousseau's signs were lacking

The results of the Wassermann and the Eagle tests were negative Examinations of urine and blood gave normal results The basal metabolic rate in June 1937 was —19 per cent On June 19, 1937 the calcium and the phosphorus (inorganic) content of the blood were 9.8 and 4.8 mg per hundred cubic centimeters, respectively, on June 30, 1937 they were 9.1 and 6.3 mg, and on July 1, 1937, they were 9.4 and 4.7 mg On June 19, 1937 the plasma chloride content of the plasma (as sodium chloride) was 632 mg, and the cholesterol content of the blood was 167 mg

Roentgenologic examination of the gastrointestinal tract made on Dec 1, 1937 showed evidence of a marked cardiospasm, the stomach appeared ptotic, but the outline was normal, a small inconstant filling defect was present in the first portion of the duodenum, probably due to a pyloric spasm, a trace of barium sulfate was seen in the stomach after six hours, the gallbladder and the appendix were not seen, there were marked ptosis and stasis in the colon

CASE 7—*Myotonia, atrophy, cataracts, baldness, possible testicular atrophy*

M. W. B., a 62 year old brother of J. B., when examined in November 1937 said that about fourteen years before he had to give up golf because he could not hold the club At about the same time he observed an atrophy of the muscles of the forearms, since that time both the atrophy and the weakness had gradually increased Four or five years ago he had noticed difficulty in relaxing his hand grasp, most evident on shaking hands For ten years or more, owing mainly to trouble with the right foot, he has had some difficulty in walking, in the last three years the left foot has become affected At the same time he has also noted a stiffness of the legs on starting to walk after he has been sitting awhile He cannot stand still without losing his balance and has to keep moving around or has to hold on to something

He is intolerant to cold, and his hands have always been bluish and cold His distant vision is good, but if he goes without glasses his eyes tire and tear They have always had "matter" in them in the morning For several years he has had nocturia and some difficulty in urination He had measles and whooping cough in childhood and mumps at 28 years of age, followed by orchitis on the left side Born in Missouri in 1875, he graduated from high school His work had been clerical and executive He is married and has a daughter, aged 29 years, alive and well One child died in infancy

Physical examination in November 1937 revealed that the patient looks very much like his brother, J. B. He has a similar build but he is much better nourished He is intelligent and cooperative and is probably telling the truth when he says he "doesn't get excited about anything" He talks with a slight suggestion of nasal twang and walks with a marked steppage gait He is bald Examination of his lenses with a hand slit lamp revealed questionable opacities The lungs and abdomen were normal The left testicle was markedly atrophic The right testicle was much larger than the left but appeared smaller than normal

The heart was not enlarged on percussion The sounds were rather faint The pulmonic second sound was louder than the aortic The blood pressure was 120 systolic and 78 diastolic, and the pulse rate, 92

When the neuromuscular system was examined it was observed that the patient had the typical myopathic facies. The temporal muscles were somewhat atrophic. The sternocleidomastoid muscles were markedly atrophic. The infrascapular and suprascapular fossae were hollowed. The deltoids were somewhat atrophied, the biceps and triceps on each side were more atrophied, and the flexors and extensors in the forearms were greatly atrophied. The hypothenar eminences were practically gone, and the thenar eminences were atrophied. Flexion and extension of the thigh and legs were good. Dorsiflexion of the feet was very weak, and the dorsiflexor muscles were atrophied bilaterally. Voluntary myotonia was present in the flexors of the fingers and the adductors of the thumbs. Mechanical myotonia was obtained in the tongue, chin muscles and muscles of the thenar and hypothenar eminences and possibly in the calf muscles. The patellar reflexes were not obtained. The Chvostek sign was not present.

CASE 8—*Myotonia, atrophy, cataracts, testicular atrophy, basal metabolic rate —30 per cent*

R. B., 27 year old son of J. B. (case 6), was born in Kansas in 1910 and had measles, whooping cough and smallpox in childhood. He has had two years of college work. He has never married. In 1927, at the age of 20 years, on throwing a ball on one occasion, the muscles of the right forearm remained in a painless cramp for several seconds. In 1928 he noticed a weakness in his hands. This weakness progressed rapidly for several years but has been about the same in the last few years. The patient says that until the last two years he had not noticed any wasting of his forearms. He has the same peculiar mental attitude as his father. He denies and minimizes all disability. It appears to be a total indifference to his body but is probably an attempt to conceal any deficiencies. In the last two years he has had a marked stiffness of his hands. This stiffness has probably been present much longer than two years, but in a milder form. It varies from day to day and is worse in cold weather, in the morning and when he contracts the muscles strongly. His legs become stiff when he stays in one position for a time, but he believes that it is no more than normal. In the last year or so he has tended to drag his feet, especially the left, and he is more likely to stumble. In the two years since he has had his teeth extracted he has had some difficulty in pronouncing certain words.

The patient dislikes cold weather. His hands and feet get cold easily and feel numb when they are cold. During the last few years he has been fatigued easily. Sweat secretion has been normal. His mouth is rather dry. His hair has been getting thinner.

He has worn glasses since 1930 when his vision became poor and he began having headaches. At present he can see well with glasses. Three years ago he got some poison weed in his eyes and since that time his eyes water and have "matter" in them in the morning.

On physical examination in January 1938 the patient was observed to be of medium height and rather slight build. He is cooperative and intelligent. His voice is definitely but not markedly nasal, and his gait is slightly "slapping." There is some ironing out of expression with a smooth, unwrinkled appearance of the skin. The hair appears to be of normal distribution and abundance. The teeth are out. The thyroid is not enlarged but is possibly more firm than normal. The lungs and abdomen are normal. Both testicles are small, soft and definitely atrophic.

Examination of the eyes revealed a marked type of chronic conjunctivitis. Until the pupil was dilated, no opacity was noted in the lens. A slit lamp examination showed some small refractile punctate dots in the subcapsular area.

near the equator of the lens in both eyes and several needle-like projections of opacity extending for a few millimeters from the equator toward the center. The vision in each eye was 20/20 with a lens correcting a moderate amount of compound myopic astigmatism.

The heart and the aorta as shown in a roentgenogram (January 1938) are of normal size and shape. The heart sounds were observed to be of normal character, and no murmurs were present. There was no evidence of peripheral sclerosis. The pulse was of good quality and of regular rhythm. The blood pressure was 100 systolic and 80 diastolic. The electrocardiogram (January 1938) showed a PR interval of 0.20 second and a slight left axis deviation.

When the neuromuscular system was examined, the muscles of expression were found to be weak, with a suggestion of myopathic facies. Atrophy of the temporal muscles was fairly marked. The sternocleidomastoid muscles were markedly atrophied. All the muscles of the shoulder girdle and upper extremities were atrophied, but the atrophy was farther advanced in the muscles of the forearm and in the thenar and hypothenar eminences than in the upper part of the arm and the shoulder. Flexion and extension of the thigh and knee were good. Dorsiflexion of the feet was weak. Voluntary myotonia was present to a marked degree in the hand grasps. Mechanical myotonia was marked in the tongue, the chin muscles, the triceps, the biceps, the flexors and extensor muscles in the forearm, the thenar and hypothenar eminences, the thigh muscles, the calf muscles and the dorsiflexors of the legs. It was present in a less degree in most of the other muscles. Electrical myotonia was obtained in all the muscles of the upper extremities, the only region examined. The triceps, patellar and achilles tendon reflexes were present. Chvostek's sign was probably negative; a twitch was obtained which appeared to be due to muscle irritation rather than to nerve stimulation. Trousseau's sign was lacking.

Reactions to the Wassermann and the Eagle test were negative. Examinations of the urine and blood gave negative results. The basal metabolic rate in January 1938 was -30 per cent. On Jan. 5, 1938 the calcium content of the blood serum was 10.1 mg. per hundred cubic centimeters, the phosphorus (inorganic) content of the serum was 4.6 mg., the cholesterol content of the blood was 143 mg., and the chloride content of the plasma (as sodium chloride) was 618 mg. A roentgenogram of the sella turcica taken on Jan. 5, 1938 showed it to be very small but of smooth outline.

Roentgenologic examination of the gastrointestinal tract on January 5, 1938 revealed a slight cardiospasm, the stomach was slightly ptotic, there was a small six hour gastric residue, the pylorus functioned normally, the gallbladder and the appendix were not definitely visualized, marked ptosis of the transverse colon was present, the colon was insufficiently filled with barium sulfate for definite diagnosis.

CASE 9—*Myotonia, atrophy, cataracts*

M. J. B., 20 year old daughter of J. B. (case 5) was examined in March 1938 in the course of the investigation of the family. She had noticed a slight stiffness in her hands in the cold since the age of 13 or 14 years. When she grasps an object such as a door knob in the cold she cannot let go readily. She does not believe that the severity of the condition has increased in recent years. She has no stiffness of the feet or jaws and no difficulty in walking. She says that she has noticed no weakness but that her fiancé says that she "seems to play out easily, sleep a lot, and doesn't seem as strong as she should." Her hands and feet are usually cold.

She has always had a high-pitched voice. She wore glasses from the ages of 7 to 12 years and started wearing them again during the last year.

Her menstrual periods started at 15 years of age, have been regular at thirty-one day intervals, and usually occur with little or no pain. Each period lasts four days, and the flow is about normal.

She had measles and smallpox in childhood. Her tonsils and adenoids were removed six years ago.

Physical examination in March 1938 showed the patient to be a somewhat undernourished, slightly built woman of 20 years. She is very active and cooperative and responds rapidly, but she attempts to minimize and conceal any defects. Her voice is irritatingly high pitched. Her gait is normal. Her jaws are narrow, with a high-arched palate and a crowding of the teeth. The thyroid is normal in size but possibly firmer than normal.

Examination of the eyes after dilation with homatropine revealed some very fine, almost dustlike highly refractile bodies throughout the periphery of the cortex of both lenses. Under the slit lamp the opacities ranged from blue and green to red. She had no other demonstrable ocular pathologic condition. Her vision in each eye was 20/20 with a correction for myopic astigmatism.

The heart and the aorta were observed to be of normal size and shape, as shown by a roentgenogram (March 1938). The blood pressure was 106 systolic and 70 diastolic. The heart sounds were normal. A systolic murmur of moderate intensity was present. It was loudest in the pulmonic area, faded somewhat in the third and fourth interspaces and increased again in intensity at the apex. The electrocardiogram (March 1938) showed a tendency to right axis deviation and a PR interval of 0.20 second. The temporal muscles were definitely weak and somewhat atrophied. The periorbital muscles were weak. The sternocleidomastoids were weak and atrophic. The triceps on each side was definitely weak, the biceps and the muscles of the forearm were questionably weak. Strength in the lower extremities was good, except possibly for weakness in the flexion of the legs. Mechanical irritability appeared increased. Mechanical myotonia was present in the tongue, chin, thenar and hypothenar eminences, flexors and extensors of the forearms and calf muscles. The biceps, triceps, abdominal, patellar, and achilles tendon reflexes were present. Trousseau's sign was absent, and Chvostek's sign was equivocal, probably negative.

CASE 10—*Myotonia, atrophy, cataracts, basal metabolic rate —10 per cent*

J. M., a 46 year old white woman, first came to the clinic in March 1936, complaining of difficulty in walking. A 31 year old sister had a cataract removed a few months previously, and another cataract was soon to be removed, a 34 year old sister (S. E., case 11) had early cataracts typical of dystrophia myotonica, her father had one cataract removed at the age of 61 years and another at the age of 64 years, a sister of her father had a cataract operation at about the age of 50 years (fig. 3).

Except for poor vision the patient was apparently well until she had typhoid fever in 1915. A year later she noticed a difficulty in opening her fist after clenching the hands tightly, a symptom which has persisted in marked degree to the present time. During the past eleven years, the hands have very slowly become weak. In the last eight years, on awaking in the morning, the patient has had difficulty in opening her eyes. The eyelids seem "heavy and stiff" and it is twenty to thirty minutes before she can keep her eyes completely open, occasionally she has to use her fingers to open her eyes. During the past nine years, if she yawns widely her lower jaw slips out of place but can be readily replaced by pressure. Three years ago weakness began in the left leg, which

she first noticed as a tendency of the leg to "stay behind" The left ankle "turns" easily, and she has great difficulty in walking up stairs

For many years she has felt weak and without energy, but in recent years this has been worse Her hands and feet are cold all the time A loss of hair, which has been noticed in recent years, has become more marked in the last two years Her vision was poor while going to school, and she began to wear glasses at the age of 24 years The vision gradually decreased, and at 34 years of age she was told that she had cataracts She had the cataract removed from the right eye in 1930 and from the left eye in 1933

She had whooping cough and measles in childhood, an appendectomy and removal of gallstones in 1919, and an operation to drain an infected toe on the left foot in 1916

Her menstrual periods started at the age of 16 years, and she said they had been regular and normal until two years ago Since that time they have become markedly irregular, and the discharge was usually excessive in amount She married at the age of 35 years and has had no pregnancies

Physical examination of the patient in March 1936 showed her to be a well nourished white woman of medium stature She is mentally alert and cooperative

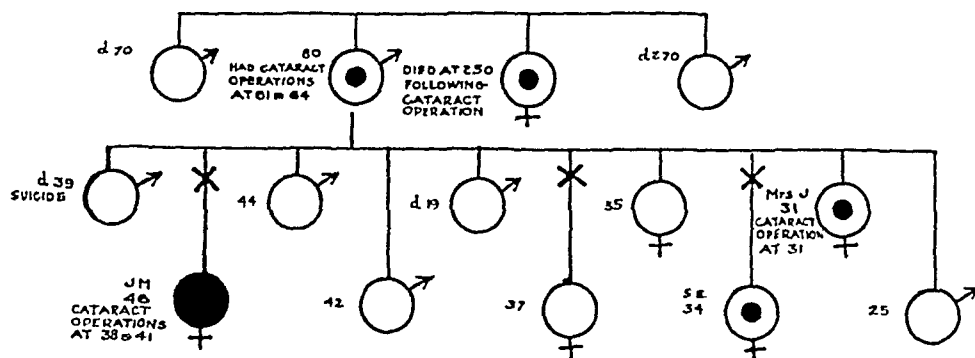


Fig 3—Family D (cases 10 and 11) The legend is the same as for figure 1

She walks with a slight limp, probably due to a "dragging" of the left leg Her voice has a nasal quality The skin of the hands is dry, shiny, cracked, rather inelastic and bluish The same is true to a less extent of the skin of her feet The thyroid is not enlarged The lungs and the abdomen showed nothing abnormal

Examination of the eyes showed a chronic blepharitis Both lenses had been removed

Except for a slight splitting of the pulmonic second sound, the heart sounds were normal in character Peripheral sclerosis was not evident The blood pressure was 116 systolic and 80 diastolic A roentgenogram taken in April 1938 revealed the heart and aorta to be of normal size and shape An electrocardiogram taken on Jan 15, 1937 showed the following characteristics very low voltage of the P waves in all leads, QRS waves of lowest voltage in lead I and notched in lead III, questionable Q waves in lead I, no Q waves but definite S waves in leads II and III, upright T waves of rather low voltage in leads I and II, inverted T waves in lead III On April 24, 1937 the following changes in the electrocardiogram were noted The voltage of the QRS waves in lead I was somewhat increased and exceeded that of lead III, no Q waves were present, but a definite S wave occurred in leads I, II and III, the ST segment was isoelectric in all leads, T₁ was now inverted, T₂ was still upright but of lower amplitude, T₃ was upright,

a Q wave was present in lead IV (Wolferth) and the T wave was upright. On April 11, 1938 the following changes were noted: QRS voltage was again lowest in lead I, but the presence of a Q_1 wave was questionable, the spread of the QRS waves was 0.11 seconds, T_1 was practically isoelectric, T_2 was somewhat greater in amplitude than on April 24, 1937, but less than on Jan 15, 1937, T_3 was practically isoelectric, T_4 was diphasic. In the period between the first two electrocardiograms, this patient had complained of shortness of breath. This was probably not as evident as it might have been if the patient had not been markedly limited in her activity by the muscular disorder. This shortness of breath gradually left, over a period of several months. It appeared likely that sometime between the first two electrocardiograms this patient had a myocardial infarction involving the anterior surface of the left ventricle. During this period the patient had received intravenous injections of a quinine salt on a few occasions, and the question arose as to the possible relationship of this medication to the electrocardiographic evidences of myocardial damage.

Examination of the neuromuscular system in March 1936 showed that the periorbital muscles, the temporal muscles and the muscles of the cheeks and mouth are weak and atrophic, typical myopathic facies being produced. The masseter muscles are weak and atrophic. The sternocleidomastoids are markedly atrophic. The trapezi, the deltoids and the muscles of the suprascapular and infrascapular fossae showed moderate weakness and some atrophy. The flexors and the extensors of the fingers are weak, atrophy is moderate. The thenar and hypothenar eminences are somewhat atrophic. Flexion of the left thigh and leg is definitely weak, and extension of the left leg is weak. This is also true to a less extent on the right leg. On both sides, dorsiflexion of the foot is weakened. Voluntary myotonia is marked in the hand grasps. Mechanical myotonia is present in the tongue, the chin muscles, the sternocleidomastoids, the deltoids, the extensors of the wrists and fingers, the muscles of the thenar and hypothenar eminences, the calf muscles and the peroneal muscles. Electrical myotonia was demonstrated in the muscles of the thenar and hypothenar eminences. The biceps, triceps, patellar and achilles tendon reflexes were not obtained.

The results of the Wassermann test and the Eagle flocculation test were negative. Several examinations of the urine and blood counts gave normal results. On March 11, 1936 the calcium content of the blood was 10 mg per hundred cubic centimeters, the phosphorus content was 3.3 mg, the cholesterol content was 230 mg, and the sugar content was 78 mg. Examination of the spinal fluid on Dec 18, 1935 showed it to be normal. The basal metabolic rate on March 10, 1936 was —10 per cent.

Fluoroscopic examination of the gastrointestinal tract in March 1938 revealed normal peristaltic waves along the course of the esophagus, the radiopaque material descended normally down the esophagus into the cardiac portion of the stomach, the stomach appeared to be of normal shape, size and position, the pylorus seemed to function normally, there was no roentgen evidence of organic disease in the stomach or duodenum and no six hour gastroduodenal residue, the gallbladder and the appendix were not definitely visualized, ptosis of the transverse colon was present.

CASE 11—*Cataracts*

S. E., aged 35 years, sister of J. M. (case 10), was examined in 1936 in the course of the investigation of the family (fig. 3). She had no complaints, and the only positive physical finding was the presence of typical early cataracts. Many small subcapsular spherical opacities, a few confluent, were found throughout the

cortex of the lens of each eye, especially toward the equator. In the beam of the slit lamp they appeared to be green and blue. The vision was 20/20 in each eye.

CASE 12—*Myotonia, atrophy, cataracts, basal metabolic rate* —20 per cent

N P, a 54 year old white man, said that his father was operated on for cataract at the age of 55 years, a brother who died at 33 years of age had a cataract operation at 30 years of age and typical muscular symptoms, a sister who died at 42 years of age had cataract operations at the age of 37 years and typical muscular symptoms, a sister aged 48 years had poor vision and marked atrophy (fig 4)

At about the age of 36 years, the patient noticed that when he started to eat, on taking the first bite his jaw would stay clamped for a few seconds before he could release it. After the first bite this would disappear. This lasted for about two years. At about the same time he noticed difficulty in releasing objects when he grasped them in his hand. Soon after, he began to have a weakness of his

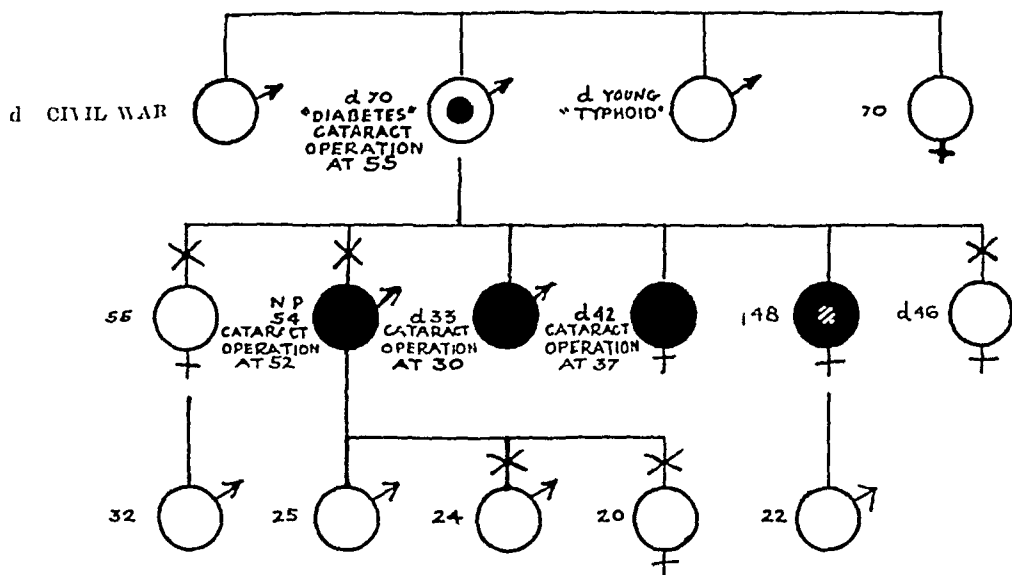


Fig 4—Family P (case 12) The legend is the same as for figure 1

hands, and he had to quit his job as a train conductor. The muscles of the hands had atrophied and become markedly weakened, especially in the last nine years. The stiffness left the fingers as they became weaker and is now present only in the thumbs. The arm muscles have also become weak and have atrophied somewhat. A "slapping" gait, which was noticed about five years ago, has shown little if any progression in the last two years. During the last few months the patient has noticed a stiffness of his legs in the morning, this leaves after he takes a few steps. For the last three years his voice has had a nasal quality, and he has noticed that in drinking from a fountain a little water at times comes back through his nose. In swallowing, at times, food seems to "stick in his throat."

In about 1925 he was told that he had a cataract. His vision gradually failed, and in 1936 he had the cataract removed from the right eye. The left eye also has a cataract. His hair started falling out at about the age of 18 years, and he was bald in his thirties.

He had typhoid fever and scarlet fever at 9 years of age, pains in the joints and fever at 32 years and influenza at 34 years. He was born in Indiana in 1884 and graduated from high school at 16 years of age. He has worked as a clerk, brake-

man, conductor and insurance salesman. He married in 1910 and has three children. He says that his libido and potency have always been normal.

Physical examination in September 1937 revealed the patient to be a well-nourished white man who appeared to have had a good muscular development at one time. He is fairly intelligent and very cooperative. He talks in a rather monotonous voice which has a definite nasal quality. He lifts his legs high as he walks and has a definite "slap" in his gait. He is bald. Examination showed the thyroid to be firm and nodular, with some enlargement of the right lobe. The lungs were normal. Abdominal examination gave negative results. The testicles were of normal size.

Examination of the eyes early in 1936, before the cataract operation, revealed a very stubborn ulcerative blepharitis of the lids and a chronic conjunctivitis. The eyes were normal except for the cataracts, which appeared as small, round, highly refractile, most frequently subcapsular opacities, throughout the cortex of each lens. A marked posterior polar cataract of the stellate variety, which gave a golden appearance with the slit lamp, was present in both eyes but was more marked in the right eye. The vision was 20/200 in the right eye and 20/40 in the left. During the following year the vision dropped to 2/60 in the right eye but remained 20/20 with a correction for hyperopia in the left eye. In December 1936 a cataract was removed from the right eye by a modified Verhoeff method, and a final visual result of 20/20 was obtained. His vision in the left eye remained about the same, now being 20/30 with a hyperopic correction.

Examination of the cardiovascular system in April 1938 showed the heart to be of normal size and shape, as revealed by a roentgenogram. The aorta was somewhat widened. The first sound was muffled and indistinct. The second was fairly well heard. There were no murmurs. The pulmonic second sound was greater than the aortic. The peripheral vessels showed no definite evidence of sclerosis. The blood pressure was 108 systolic and 74 diastolic. The electrocardiogram showed a PR interval of 0.26 second and a QRS spread of 0.14 second, with the form of a left bundle branch block.

On examination of the neuromuscular system in September 1937 the temporal muscles were shown to be somewhat atrophic, and the periorbital muscles, the orbicularis oris and the cheek muscles all very weak, the typical myopathic facies being produced. The patient cannot open his mouth widely. The sternocleidomastoid muscles are markedly atrophied. The deltoid, the muscles of the infra-scapular and suprascapular fossae and the triceps are weak and somewhat atrophied. The biceps on each side and the pectoral muscles are of fairly good strength. Both the flexors and extensors of the forearm are markedly atrophied. The small muscles of the hand, including the interossei, are atrophied. Dorsiflexion of both feet is weak. The muscles of the thenar eminence show active myotonia. Mechanical myotonia is obtained in the thenar and hypothenar groups of muscles, the calf muscles and the glutei. Electrical testing shows a typical myotonic reaction in the thenar and hypothenar muscle groups. The biceps, abdominal and patellar reflexes are present. The achilles tendon reflexes were not obtained. Chvostek's sign is absent.

The results of the Wasseimann and the Eagle flocculation test were negative. Several examinations of the urine and blood counts gave normal results. The basal metabolic rate in January 1936 was —16 per cent, and in July 1936 it was —20 per cent. The calcium and phosphorus (inorganic) contents of the serum as determined on several different occasions was as follows (in milligrams per hundred cubic centimeters): Jan 20, 1936, calcium 9.2, phosphorus 3.9, July 20, 1936, calcium 10.6, phosphorus not determined, July 21, 1936, calcium 10.0,

phosphorus 54, July 25, 1936, calcium 111, phosphorus not determined, Nov 22, 1937, calcium 90, phosphorus 30 On July 20, 1936, the cholesterol content of the blood was 154 mg per hundred cubic centimeters, and the chloride content (as sodium chloride) was 522 mg per hundred cubic centimeters

The moist weight of the lens removed in December 1936 was 0.1823 Gm The lens was immediately ground up with sodium sulfate, dried for twenty-four hours in an incubator and then extracted with chloroform The cholesterol content of the lens was 112 mg per hundred cubic centimeters, or 0.614 per cent of the moist weight of the lens

Roentgenologic examination of the gastrointestinal tract in April 1938 revealed normal peristaltic waves in the esophagus, the stomach appeared to be of normal shape and position, a constant defect was seen in the pyloroduodenal region, the pylorus did not appear to be unusually patent, about one fifth of the barium sulfate meal remained in the stomach after six hours, the gallbladder and the appendix were not definitely visualized, there was some spasticity of the colon, but there was no definite roentgen evidence of organic disease

CASE 13—Myotonia, atrophy, cataracts, baldness, basal metabolic rate —26 per cent

F B, aged 44 years, was examined in April 1938 The patient's father died at 75 years of age in a state hospital to which he had been committed with a diagnosis of senile dementia The patient said that his father wore glasses for many years and that for a number of years before his death his vision was so poor that he could not use a mirror to shave himself The patient's mother was mildly diabetic and died at 81 years of age One sister in her fifties had diabetes and, according to the patient, had difficulties with her eyes and legs Another sister died in her fifties, she once told the patient that her hands "stuck to things" At the time this paper was written there were several other brothers and sisters whom we hope to examine in the future

At about the age of 16 or 17 years, the patient first noticed that if he gripped an object strongly he would have difficulty letting go This difficulty in relaxing his grip gradually became worse At 22 to 23 years of age he noticed that his grip was not as strong as that of his fellow workers Since that time there had been a gradual loss of strength in his grip, and in the last three years it was noticed that the weakness was marked The strength in his arms and shoulders also decreased He said that about two years ago people called his attention to the fact that he walked as though he had a "wooden leg or was paralyzed" Since that time he had been conscious of an increasing difficulty in walking During the last year a stiffness of the ankles on starting to walk had been present He had recently been tiring with very little exertion

In the last six months his voice had become lower in pitch, less clear and somewhat husky Occasionally he had difficulty in drinking water from a fountain

His hands and feet had been cold as far back as he could remember Print blurred when he read, and his eyes frequently burned and watered

The patient had had mumps, with no associated orchitis He had typhoid fever at 14 and pneumonia at 22 years of age At the age of 30 years he was in the hospital with a pain in the right side, which was attributed to a ureteral stricture He had gonorrhea at 22 years and again at 33 years of age, after the second attack he had some pains in the joints and swelling He married at the age of 22 and has been divorced for about ten years He has had no children, although he said his wife was pregnant on several occasions and induced abortions

Physical examination in April 1938 of the patient revealed him to be a tall well nourished white man of 44 years He is intelligent and cooperative His voice is

definitely nasal, and his gait is of "steppage" nature. He is bald, with a graying rim of hair. Most of the teeth are present, although in poor condition. The thyroid is small but very firm. The results of examination of the lungs and abdomen were negative. Both testicles were possibly somewhat softer and smaller than normal.

The examination of the eyes showed a slight marginal blepharitis and a chronic conjunctivitis. Slit lamp examination after the introduction of homatropine hydrobromide showed many fine opacities, varying in size from that of a dust particle to almost a millimeter in diameter. The opacities were scattered throughout the cortex of the lens, extending well into the central area. They were a grayish white, but refractile, and appeared blue and blue-green at times. The fetal nucleus was not involved. Vision with glasses was 20/20 in both eyes.

The heart and aorta were normal, as shown by roentgenologic examination (April 1938). The blood pressure was 96 systolic and 64 diastolic with the patient in the recumbent position and 104 systolic and 72 diastolic when he was in the sitting position. The systolic pressure fell about 10 mm with deep inspiration. The heart sounds were somewhat faint but normal in character. The aortic second and the pulmonic second sound were of about equal intensity. No murmurs were heard. Peripheral sclerosis was not evident. The electrocardiogram (April 1938) was normal except for a somewhat high take-off of the ST segment in lead I (1 mm) and in lead II (1 mm).

The temporal muscles were markedly atrophied, and the masseter muscles were somewhat atrophied. The periorbital muscles and the orbicularis oris were weak. The sternocleidomastoids were almost completely atrophied. The muscles of the supraclavicular fossae and the deltoids were somewhat atrophied. The biceps and especially the triceps on each side were weak and somewhat atrophic. Both the flexor and the extensor muscles in the forearm were very weak and atrophic. The muscles of the thenar and hypothenar eminences were only slightly involved, but the interossei were definitely atrophied. Flexion and extension of the thigh were fairly good, as was extension of the knees. Flexion of the knees was weakened. Plantar flexion of the feet was fair on the left and weak on the right. Dorsiflexion of the feet was markedly weakened. Voluntary myotonia was present in the movements of the fingers and thumbs and in the ankle movements. Mechanical irritability of the muscles was increased in most regions. Mechanical myotonia was present in the tongue, chin muscles, deltoids, biceps and triceps on each side, the flexors and extensors in the forearm, the muscles of the thenar and hypothenar eminences, the quadriceps on each side and the left gastrocnemius. The patellar and the abdominal reflexes were present and normal. The biceps and achilles tendon reflexes could not be obtained. Chvostek's sign was positive. Trousseau's sign was negative.

The results of the Wassermann and the Eagle test were normal. Examination of the spinal fluid gave normal results. On April 25, 1938 the calcium content of the blood serum was 9.3 mg per hundred cubic centimeters, and the phosphorus content was 2.8 mg. The basal metabolic rate was -26 per cent, and the cholesterol content of the blood was 148 mg per hundred cubic centimeters.

Important features of dystrophia myotonica brought out by the foregoing case histories will be discussed in the following order: (1) hereditary features, (2) onset, (3) myotonia, (4) atrophy, (5) cataracts, (6) endocrine and metabolic changes, (7) mental changes, (8) cardiovascular system and (9) gastrointestinal system.

HEREDITARY FEATURES

The hereditary features of dystrophia myotonica are of the greatest importance, because they throw much light on the nature of the disease and help to differentiate it from other hereditary disorders of the neuromuscular system as well as from the more closely related hereditary disorder myotonia congenita (Thomsen's disease).¹ Fleischer,¹ Henke and Seeger⁸ and others who have studied the heredity of this disease, including two of us (A. R. and J. J. W.),⁹ have stated the belief that it is transmitted as a dominant. Unlike such a character, however, the determiner for dystrophia myotonica may apparently be present without manifesting itself, as indicated by the frequency with which the parents of our patients appeared to be normal and by the occurrence of isolated cases of dystrophia myotonica which can be traced back several generations to a common ancestor. Although dominant genes need not affect every generation, the large number of unaffected parents is not to be explained solely in this manner. To clarify this apparent inconsistency, geneticists have utilized the concept of "progressive inheritance." In diseases which exhibit progressive inheritance, the onset of the disease is at an earlier age in successive generations (anticipation). The disease also may become increasingly severe in successive generations (potentiation). In the light of this concept one may interpret the inheritance of dystrophia myotonica as follows. It is due to a dominant mutation which is at first manifested by very few signs, because of the mildness of the condition or because the patients do not live long enough to show many of the signs. In successive generations the disease sets in at an earlier age and increases gradually in severity until, finally, the full-blown syndrome of dystrophia myotonica can be recognized.

This interpretation of the course of events receives important confirmation from two sources. The first is the common occurrence of cataract, one of the most important signs of the disease, in the generations preceding the definitely dystrophic generation. Fleischer has shown that the occurrence of this cataract presents also the remarkable phenomenon of anticipation, that is, the age of onset is earlier in each succeeding generation. In antecedent generations occur senile cataracts, in later generations, presenile cataracts, in the definitely dystrophic generation the cataracts may occur in youth. The second source is the earlier age of onset of the disease in the dystrophic children of

8 Henke, K., and Seeger, S. Ueber die Vererbung der myotonischen Dystrophie. Genetischer Beitrag zum Problem der Degeneration, *Ztschr. f. d. ges. Anat.* (Abt. 2) **13** 371, 1927.

9 Ravin, A., and Waring, J. J. Studies in Dystrophia Myotonica. I. Hereditary Aspects, *Am. J. M. Sc.* **197** 593, 1939.

dystrophic parents By fairly exhaustive investigation of the literature 32 instances were found in which both parents and children were affected, in every one of these the age of onset of the disease in the children was at an earlier age than in the parents

The foregoing interpretation may be summarized as follows The disease appears to be due to a dominant factor which is at first manifested by no signs or by very slight signs notably cataract In those families in which cataract occurs its onset at an earlier age in succeeding generations is evidence of the defective gene Finally, in one generation the complete syndrome of dystrophia myotonica appears Persons with the disease now transmit it to their children as a simple dominant The onset of the disease in the children is at an earlier age than in the parents, until finally a generation occurs in which the onset is before maturity, and the disease ceases to appear in that family

It seems probable that the defective gene appears first in a family by mutation One may conclude with McFarland and Meade¹⁰ that "the cause of mutation or suddenly appearing striking variation is unknown It or something comparable to it, may occasionally modify the germ plasm in such a manner as to result in congenital deformity insanity, dyscrasia, metabolic disturbance or tumor Once changed by mutation, the germ plasm may carry the newly acquired character through many generations or may end it with one generation, when it results in a state incompatible with the propagation of its abnormal kind "

ONSET

The onset of dystrophia myotonica has usually been stated to be in the third or fourth decade From what has been said about the heredity of the disease it is evident, however, that the age of onset will vary markedly with the generation affected The disease is likely to be first recognized in the generation in which the onset is in the third or fourth decade of life, because in the preceding generation the disease begins at a later age and only rarely progresses to a point where the diagnosis is made before death The presence of cataract in one of the parents of a patient with dystrophia myotonica might in retrospect be considered as evidence that that parent had the disease although the muscle symptoms had not progressed to the point where the diagnosis is made The children of a person in whom the disease began in the third or fourth decade may show the disease in the second or even the first decade of life (cases 5 and 9)

10 McFarland J, and Meade, T S The Genetic Origin of Tumors Supported by Their Simultaneous and Symmetrical Occurrence in Homologous Twins, *Am J M Sc* 184 66, 1932

One of the most impressive features of the disease is the insidiousness of its onset and the slowness with which it progresses. From the patients' histories and from the observation of several patients over a period of more than three years, we feel that degenerative signs are present for many years before they attract the patient's attention. The apparent insensibility and indifference of these patients to their physical disabilities are undoubtedly due in part to the insidious manner in which the disease develops. Since they are perhaps honestly unaware of the earliest muscular changes, the time of onset of the disease is apt to be underestimated by many years.

It is not possible in every instance to identify the initial symptom among the many dystrophic features of the disease. Usually one dystrophic feature appears either to have preceded the others or to have progressed more rapidly. From the histories of the patients of this series, myotonia appears to have been the first symptom in 5 patients, muscle weakness and atrophy in 4 patients and cataract in 3 patients, in 1 patient myotonia and atrophy began at the same time. It is possible however, that myotonia may be, as many believe, the earliest symptom, but since it is not as disabling as the atrophy, the patient's attention is not attracted to it. Thus, the presenting complaint is usually the result of the muscular weakness, even when myotonia preceded the weakness by many years. The observation that in 2 of our patients cataract was present without the other symptoms having yet become of sufficient severity to be recognized would indicate that cataract is often the earliest evidence of the condition.

The sex incidence in the 5 patients presenting themselves for examination was 4 men and 1 woman. In the entire group of 13 patients, it was 8 men and 5 women. If to these 13 patients are added 5 patients who were not examined but who in our opinion, based on a study of the family histories, undoubtedly had the disease, the sex incidence becomes 10 men and 8 women. This is close to the 1 to 1 ratio expected on hereditary grounds.

MYOTONIA

After contraction, the myotonic muscle persists in a state of contraction, from which it relaxes slowly to resume its resting state, only after thirty seconds or more in some patients. The contraction persists after the stimulus producing it has ceased to act and appears, therefore, as a slowness or delay in relaxation. In contrast to myotonia congenita (Thomsen's disease), in which the myotonia is generalized and the only cause of disability, the myotonia in dystrophia myotonica is limited in distribution and overshadowed in importance by the progressive

muscular atrophy The myotonia is, however, so characteristic that it deserves emphasis because of its great diagnostic value

Myotonia occurs most commonly in the muscles of the forearms and hands, where it is manifested by an inability to relax promptly, easily, and naturally the hand clasp, to "let go" any object firmly grasped One of our patients, a railroad brakeman, nearly lost his life because of his inability to "let go" the iron handle on a box-car A younger patient could not relax his grip "frozen" to his golf club after a stroke A carpenter after driving a few nails could not lay down his hammer A housewife found pulling weeds a slow process because of an inability to "let go" a weed pulled with difficulty from the ground Greenfield wrote of a physician with this malady who found himself under suspicion because of his suggestively caressing hand clasp when shaking hands with his women patients Myotonia also occurs at times in the muscles of mastication, as indicated by a curious difficulty on starting to talk, chew or swallow, and in the muscles of the legs, as indicated by "stiffness" of the muscles and joints on starting to walk or run or get up from a cramped position

When the muscular contraction is voluntary, as in the aforementioned instances, we have used the term "voluntary myotonia", if the muscle is stimulated to contract by mechanical or electrical means we have used the terms "mechanical myotonia" and "electrical myotonia"

The prolonged contraction characteristic of myotonia is easily distinguished from simulating conditions by the following properties

- 1 The difficulty in relaxing the contracted muscle becomes less with each repetition of the contraction, and after several contractions the relaxation occurs with apparently normal rapidity The difficulty in relaxation is accordingly most evident after a period of rest If the patient is instructed to open and close his fist repeatedly and as rapidly as possible, the first few movements are performed slowly and with difficulty, but with each repetition the movement becomes more facile, until it is carried out with apparent normal rapidity If, however, the patient rests for a while, the difficulty returns

- 2 Myotonia is not painful

- 3 Myotonia increases in degree, up to a limit, with increase in the force of contraction M J B (case 9) could open and close her fist without noticeable difficulty, but after squeezing the dynamometer she could release it only with effort

- 4 The contractions which show myotonia are voluntarily produced contractions Involuntary contractions occur only rarely in diseases associated with myotonia and then represent an accidental association

Voluntary myotonia has been markedly decreased by the administration of quinine³ and to a less extent by the administration of

epinephrine¹¹ It has also been somewhat decreased by calcium, given intravenously¹¹ The administration of insulin produced a decrease when symptoms of hypoglycemia were present, and it was probable that the decrease depended on the mobilization of epinephrine¹¹ The administration of prostigmine aggravated myotonia, and the administration of potassium chloride has been reported to aggravate it¹² Warmth usually decreases myotonia, and cold increases it Possibly by increasing involuntarily the strength of contraction, excitement and fight increase myotonia

Mechanical myotonia is most easily demonstrated by striking the muscle with a percussion hammer In the case of large muscles, a lingering furrow or dimple is produced by the persistence of the contraction of the stimulated muscle fibers Smaller muscles, such as those of the thenar and hypothenar eminences, may contract as a whole Mechanical myotonia is usually more widespread than voluntary myotonia Its presence in the tongue is especially constant and worthy of note The muscles commonly involved are listed in table 1

The response of myotonic muscles to electrical stimulation is very characteristic The essential feature is the persistence of the contraction after cessation of the stimulating current, but the details of the response of the muscles and nerves to faradic and galvanic currents are too complex for the present discussion The typical myotonic response is complicated by the presence of atrophy in many of the muscles The total reaction of the muscle to mechanical and electrical stimulation was called by Erb¹³ the "myotonic reaction"

ATROPHY

The atrophy is characterized by a typical pattern of involvement, which includes the muscles of the face, the sternocleidomastoids, the muscles of the forearm, the quadriceps and the dorsiflexors of the foot The muscles in one or more of these locations usually show the initial involvement, but when the condition is moderately advanced the entire group is more or less affected Atrophy may affect muscles which are or have been myotonic, or it may affect muscles which apparently have shown no myotonia

In the face, the muscular involvement results in the so-called myopathic facies, consisting of temporal hollows, sunken and sagging cheeks, drooping mouth corners and a persistently glum expression The orbicularis oculi of each side, the orbicularis oris and the temporal muscles are early affected Atrophy and weakness of the pharyngeal

11 Ravin, A Studies in Dystrophia Myotonica III Experimental Studies in Myotonia, Arch Neurol & Psychiat **43** 649 (April) 1940

12 Russell, W R, and Stedman, E Observations on Myotonia, Lancet **2** 742, 1936 Kennedy and Wolf^{2a}

13 Erb, W H Die Thomsen'sche Krankheit, Leipzig, F C W Vogel, 1886

TABLE I—Summary of Cases

TABLE 1—Summary of Cases													
Case number	Patient	Age and sex	Evidence of heredity	Probable age of onset	Myotonia	Atrophy	Cataract	Active myotonia	Hand grasp	Jaw	Legs	Mechanical myotonia	Thenar
1	O M	43, M	+	33	27	30	+	+	+	+	+	+	+
2	N M	59, F	+	52	57	16	+	+	+	+	+	+	+
3	J L	56, F	+	45	55	52	+	+	+	+	+	+	+
4	O M	53, M	+	48	+	+	+	+	+	+	+	+	+
5	H M	22, M	+	20	0	0	0	0	0	0	0	0	0
6	J B	60, M	+	47	60	+	+	+	+	+	+	+	+
7	M W B	62, M	+	57?	48?	?	+	+	+	+	+	+	+
8	R B	27, M	+	25	18	27	+	+	+	+	+	+	+
9	M J B	20, F	+	13	?	20	+	+	+	+	+	+	+
10	J M	16, F	+	23	33	34	+	+	+	+	+	+	+
11	S E	35, F	+	35	0	0	0	0	0	0	0	0	0
12	N P	54, M	+	36	36	41	+	+	+	+	+	+	+
13	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
14	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
15	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
16	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
17	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
18	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
19	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
20	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
21	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
22	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
23	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
24	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
25	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
26	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
27	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
28	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
29	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
30	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
31	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
32	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
33	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
34	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
35	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
36	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
37	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
38	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
39	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
40	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
41	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
42	F B	44, M	+	16	22	41	+	+	+	+	+	+	+
43	F B	44, M	+	16	22	41	+	+	+	+	+	+	+

muscles also occur early and produce a nasal voice, poor enunciation and an easily fatiguing voice. The masseter muscles may be involved and with the weakened temporal muscles may result in a tendency to easy dislocation of the lower jaw. Atrophy of the tongue is late.

The involvement of the sternocleidomastoids is early and remarkably constant. In moderately advanced stages of the disease only a few fibers of the muscles may be present. The weakness is nicely demonstrated by asking the patient to sit up from the supine position. When the involvement is severe the head of the patient tends to fall back and is often supported with the hand.

The atrophy and weakness of the muscles in the forearms are especially incapacitating and frequently the presenting complaint. Of the flexor muscles, the superficial and deep flexors of the fingers and the long flexors of the thumbs are markedly involved. The flexors of the wrist show less involvement, and patients with this condition soon learn to depend on the wrists to lift objects. The extensor muscles are usually more markedly and universally affected than the flexor. The muscles of the thenar and hypothenar eminences do not show marked involvement until late, and the adduction and opposition of the thumb are therefore often strong after flexion of the fingers is almost gone. Since myotonia tends to disappear as the muscles atrophy, it may be evident in advanced stages of the disease only in the movement of the adduction and opposition of the thumb. In some patients the interossei muscles are involved early. The hand tends to assume a position resembling a cone, the palm is contracted, and the fingers are bent at the metacarpophalangeal joints, with their tips coming together to form the apex of the cone.

In the lower extremities, the dorsiflexors of the foot are early affected, with the production of a foot drop and a steppage gait. When the quadriceps femoris becomes weak, the difficulty in walking is great. The patient is unable to raise the leg high enough to overcome the foot drop, and the risk of falling is great.

As the disease progresses, other muscles become weak and atrophied. In the far advanced conditions, most of the muscles of the body are involved, and the patient is markedly emaciated.

The atrophy is not associated with fibrillary twitching. The tendon reflexes are not abnormal but disappear as the muscles atrophy. At times the weakness and atrophy of the muscles of the lower extremities, especially in the early stages, are associated with pain, usually described as aching. Although Maas¹⁴ in a recent report stated that the vibratory sense was found diminished in many persons with dystrophia myotonica, sensory disturbances are otherwise lacking.

14 Maas, O. Disturbances of Sensibility in Dystrophia Myotonica, *Brain* 61: 449, 1938.

CATARACTS

Of the 13 patients in our series, 12 had cataracts. The 1 patient who did not appear by slit lamp examination to have cataracts had such slight evidence of the disease that it was only on the basis of the family history that the diagnosis could be made. Two patients, furthermore, had cataracts without any definite muscle changes. It may be concluded, therefore, that the presence of cataracts on slit lamp examination is one of the earliest and most constant features of dystrophia myotonica. The importance of the occurrence of cataracts in the ancestors of patients has already been emphasized.

On slit lamp examination of the lens, the characteristic observations are as follows: 1. Small regular opacities are found in the cortex of the lens, especially under the capsule. These opacities are highly refractile, appearing blue, blue-green and yellow. 2. A posterior sub-capsular star-shaped opacity may be present very early, although no patient in our series had such a lesion before the punctate opacities were demonstrable. This is an opacity similar to that found in other forms of complicated cataract. 3. The cataracts develop very slowly, taking ten to twenty years to mature. The mature cataract, the punctate opacities having become confluent, is indistinguishable from other types of mature cataracts.

Although the cataract in its early stages almost always shows the changes just described, a diagnosis of dystrophia myotonica cannot be established on the evidence of the lenticular changes alone, as tetany, among other conditions, may produce somewhat similar changes. Several cataracts not unlike this type have been seen in patients in whom no etiologic factor could be established. Although the diagnosis of dystrophia myotonica cannot be made on the lenticular changes alone, it is evident that if a typical cataract is found in a person with a family history of dystrophia myotonica, that person has dystrophia myotonica as surely as his brother or sister who shows only muscular changes.

The cholesterol content of the lens removed from N. P. (case 12), by the intracapsular method, was 0.614 per cent of the moist weight. This is well within the limits for cholesterol content in lenses with mature cataracts of all types, as found by Salit and O'Brien,¹⁵ namely 0.239 to 0.679 per cent, with an average of 0.512 per cent.

A chronic ulcerative type of blepharitis and chronic conjunctivitis was present in 9 patients and absent only in the 4 patients showing the least degenerative change. This rather constant observation has been mentioned only occasionally in other reports.

15 Salit, P. W., and O'Brien, C. S. Cholesterol Content of Cataractous Human Lenses, *Arch. Ophthalm.* **13**: 227 (Feb.) 1935.

ENDOCRINE AND METABOLIC CHANGES

The endocrine system of the body shows evidences of generalized and often marked involvement. Testicular atrophy is frequent (in 3 of the 8 men in this series), and when marked it results in impotence and infertility. Involvement of the ovaries is indicated by the frequent occurrence of menstrual irregularities and the marked infertility of women with the disease. The thyroid is often enlarged and of increased firmness. The basal metabolic rate is usually low, in the 7 patients of this series for whom estimations were made, it ranged from — 11 per cent to — 41 per cent with an average of — 25 per cent. The cholesterol content of the blood, on the other hand, was normal in every instance in which it was determined.

The resemblance of myotonia to tetany, the frequently reported presence of Chvostek's sign and even of Trousseau's sign and the almost invariable presence of cataract have suggested to many a hypofunction of the parathyroid glands. Against a hypofunction of the parathyroids may be mentioned the following facts: 1. Even superficial comparison of myotonia and tetany suffices to show that they are in no way related. In contrast to tetany, which is frequently painful, occurs spontaneously and is localized mainly in the extremities in the same pattern, myotonia is not painful, occurs always in connection with certain voluntary movements and cannot be produced by pressure on the nerve trunk or large vessels. 2. The calcium and phosphorus values in the blood are practically always normal, as they were in this series. 3. It is our feeling that what has usually been reported as Chvostek's sign is really produced by the direct stimulation of the hyperirritable facial muscles, rather than by a stimulation of a hyperirritable nerve. The former phenomenon was observed in several patients, but in only 1 patient was a true Chvostek sign obtained. Trousseau's sign was not obtained in any patient.

The conception of the pituitary as the master regulator of the endocrine system leads to the suggestion of a primary hypofunction of the pituitary as the fundamental cause of many of the changes. The low basal metabolic rate, the testicular and ovarian dysfunction, the general body emaciation and the alopecia observed in this series lend some plausibility to this suggestion.

Sugar tolerance tests on many of our patients failed to reveal the presence of any abnormality of carbohydrate metabolism. This work will be reported later.

Many studies of creatine excretion in myotonia congenita and dystrophia myotonica have failed to show any connection between the myotonia and creatine excretion. Abnormal creatinuria may be present when the muscle wasting is marked, but it is less than that seen in pro-

gressive muscular dystrophy¹⁶ Studies on creatinine and creatinine excretion in 3 of the aforementioned patients also will be reported later

MENTAL CHANGES

Maas and Pateison¹⁷ examined psychiatrically 29 patients with dystrophia myotonica They found 17 of them to be of low intelligence, 11 on a congenital basis and 6 as a result of deterioration They also found 6 patients who presented clinical pictures in some respects resembling classic syndromes of mental disorder They felt that marked muscular wasting was associated with mental changes A definite temperament was found by them in so many patients as to seem almost characteristic of the disease It consisted in persistent and almost morbid cheerfulness, mild grandiosity and a lack of drive and initiative

Our experience does not parallel that of Maas and Pateison Whether it is as the result of hereditary defects or as the result of injurious prenatal and postnatal influences, a large percentage of mental defectives is found in many affected families In other families, however, mental defects appear to be slight or absent This was true in most of our cases A careful study of our patients for the presence of mental deterioration is in progress and will be reported later The characteristic temperament which Maas and Pateison described occurred infrequently, and those changes in temperament which were found seemed more of a reaction to body defects than the result of any special congenital or degenerative mental change

CARDIOVASCULAR SYSTEM

Guillain and Rouquès¹⁸ and d'Antona¹⁹ have called attention to the high percentage of cardiovascular abnormalities in the small series of patients with dystrophia myotonica in whom the cardiovascular system has been adequately studied These authors suggested the possibility that the cardiovascular system was also involved in the dystrophic process but cautiously stated that no conclusion must be drawn until

16 Milhorat, A. T., and Wolff, H. G. Studies in Diseases of Muscle. V. Metabolism of Creatine and Creatinine in Myotonia Congenita, Myotonia Atrophica, Amyotonia Congenita, Dystonia Musculorum Deformans and Paralysis Agitans, *Arch Neurol & Psychiat* **40** 680 (Oct) 1938

17 Maas, O., and Paterson, A. S. Mental Changes in Families Affected by Dystrophia Myotonica, *Lancet* **1** 21, 1937

18 Guillain, G., and Rouquès, L. Le cœur dans la myotonie atrophique, *Ann de méd* **31** 158, 1932

19 d'Antona, L. Osservazioni sullo stato dell'apparato circolatorio e digerente nella distrofia miotonica. La sindrome endocrina ed umorale, *Minerva med* **1** 833, 1935

a larger series of cases have been studied. The abnormalities which have been noted by various workers include the following: hypotension, bradycardia, peripheral vasomotor disturbances, fluoroscopic and roentgenographic abnormalities and abnormalities of the electrocardiogram.

A large percentage of patients with dystrophia myotonica have blood pressures somewhat lower than average, and our impression from the reading of many case reports has been that hypertension is rare. In our series 5 patients (cases 1, 6, 8, 12 and 12), all with fairly advanced dystrophia myotonica, had what might be considered hypotension. Two patients (cases 5 and 9), not seriously affected, had low, but possibly average, blood pressures. Two other patients with marked involvement had blood pressures which might be considered low for their age, M W B (case 7) 120 systolic and 78 diastolic at 62 years of age and J M (case 10) 116 systolic and 80 diastolic at 44 years of age.

The presence of bradycardia, which has often been observed and reported by others, is evident on examination of table 2.

Most of our patients complained of cold hands and cold feet and showed a more or less marked degree of cyanosis of the hands under the influence of mild cold.

None of the patients in this series had roentgen evidence of an enlarged heart, and except for some widening of the aorta in N P (case 12) no abnormality was found in the roentgenograms of the chest. This corresponds to the lack of significant changes in the size or shape of the heart found by most observers.

On auscultation, the heart except in 2 patients seemed normal. In our series a systolic murmur was heard in J B and M J B (cases 6 and 9). In M J B (case 9) the nature of the murmur and the absence of a rheumatic history suggested the possibility of a congenital heart lesion.

The percentage of our patients showing electrocardiographic abnormalities is surprisingly large and agrees in this respect with the observations of Gullian and Rouquès. Electrocardiograms were taken of 8 patients. Two patients (cases 6 and 9) were definitely normal, 1 patient (case 13) was normal except for a slightly high take off of the ST segments in lead I (1 mm) and lead II (1 mm), R B (case 8) showed a slight left axis deviation, and N M (case 2) showed a more marked left axis deviation, O M (case 1) had a low voltage and a PR interval of 0.23 second, N P (case 12) had a PR interval of 0.26 second and a left bundle branch block, J M (case 10) during the period of observation showed definite evidence of a myocardial infarction.

The large number of patients who showed abnormalities in the electrocardiogram is even more surprising when it is remembered that

hypotension was observed to be common and that peripheral sclerosis was slight in most patients. Nevertheless, the type of change observed would suggest coronary sclerosis rather than a dystrophic process involving the myocardium.

TABLE 2—Summary of Cardiovascular Examinations

Case	Age	Severity of Disease	Blood Pressure	Pulse During B M R	Results of Examination	Evidence of Peripheral Sclerosis	Cold Cyanotic Hands	Electrocardiograms
1	43	++	100/68	56	Normal on roentgen examination and auscultation	0	+	Low voltage of P waves PR = 0.24 sec. low voltage of QRS waves, largest excursion 5 mm
2	59	++	138/90	70	Normal on roentgen examination and auscultation	?	+	PR = 0.20 moderate left axis deviation
3	56	+	122/80	80*	Normal on percussion and auscultation	0	+	Not done
4	53	Slight	130/80		Normal on percussion and auscultation	0	0	Not done
5	22	Slight	108/68		Normal on percussion and auscultation	0	0	Not done
6	60	-++	104/70	72	Normal on roentgen examination, rough, loud systolic murmur at apex	Slight	+	Normal ekg
7	62	++-	120/78	92*	Normal on percussion and auscultation	?	-	Not done
8	27	++	100/80	49	Normal on roentgen examination and auscultation	0	+	PR = 0.20 slight left axis deviation
9	20	+	106/70		Normal on roentgen examination, systolic murmur, loudest in pulmonic area	0	-	Tendency to right axis deviation
10	46	++-	116/80	58	Normal on roentgen examination and auscultation	0	+	Evidence of coronary changes
12	54	++-	108/74	50	Aorta somewhat widened on roentgen examination, indistinct first heart sound	+	+	PR = 0.26 seconds left bundle branch block
13	44	+-	96/64	60	Normal on roentgen examination and auscultation	0	+	Slightly high take off of ST segment in lead I (1 mm) and lead II (1 mm)

* Not during determination of the basal metabolic rate

GASTROINTESTINAL TRACT

d'Antona¹⁹ reported that fluoroscopic examination of the gastrointestinal tract in 1 patient suggested the occurrence of myotonic phenomena in the esophagus and possibly in the stomach. We did not observe a similar phenomenon in any of the 7 patients in this series who had roentgenographic and fluoroscopic examinations of the gastrointestinal system.

DIAGNOSIS

The disease must be differentiated from myotonia congenita (Thomson's disease), from the various progressive muscular atrophies and dystrophies, from other diseases producing presenile cataracts and from various endocrine disorders

The hereditary nature of the disease is of the greatest diagnostic importance, atrophy occurs in a typical pattern, myotonia is characteristically limited in distribution, cataract occurs at an early or middle age, associated testicular atrophy is most significant, and finally, a low basal metabolic rate is commonly present

TREATMENT

It is one of the distinguishing features of the heredodegenerative diseases, of which dystrophia myotonica is a member, that they increase slowly and inexorably in severity. The insidiousness with which the disease sets in and the slowness with which it progresses have been described. The progression of the disease is almost imperceptible to close friends and relatives. It is this slowness of progression which makes evaluation of any treatment most difficult. Treatment which merely halted the progression of the disease would have to be used for many months or years before one could be sure of its effect. Only if the drug produced a dramatic change in the patient's condition could one be sure of a beneficial therapeutic effect. The possibility of the spontaneous occurrence of periods during which the progression of the disease stops or during which even improvement may occur further complicates the evaluation of treatment.

The type of change, degeneration, makes treatment exceedingly difficult. The greatest benefit obviously could be obtained by prevention—by voluntary celibacy of members of affected families or by voluntary contraception¹. After the degenerative changes are present, little can be expected from treatment. An atrophied muscle or an atrophic testicle cannot be replaced, nor a clouded lens cleared¹.

Treatment is further complicated by the number of tissues affected. If the widespread involvement is due to the absence of one specific substance, a hormone for example, the ideal treatment would be substitution therapy. Although it is possible that all changes may be due to a single deficiency, positive evidence as to its nature is lacking. In the absence, therefore, of specific substitution therapy, the symptoms must be treated individually.

MYOTONIA

Treatment of the myotonia is discussed first, because it has been the most satisfactory. In 1936 Wolf^{2c} reported the great improvement in myotonia produced by quinine. This observation has since been amply confirmed. Given by mouth, in doses of 15 to 30 grains (0.97

to 1.94 Gm) daily, quinine temporarily abolishes almost all evidence of the myotonia. Quinine has not been shown, however, to have any effect on the muscular weakness and atrophy. Since patients with dystrophia myotonica, unlike patients with myotonia congenita, are not especially incapacitated by their myotonia and usually seek medical advice because of muscle atrophy or cataract, quinine generally does little to correct the original complaint. Thus, of the 6 patients receiving quinine (O. M. [case 1] 10 to 20 grains [0.65 to 1.29 Gm] daily for two months, N. M. [case 2] 10 grains [0.65 Gm] daily for five weeks, J. B. [case 6] 15 grains [0.97 Gm] daily for four weeks, R. B. [case 8] 5 grains [0.32 Gm] three times daily for one month, J. M. [case 10] 10 to 20 grains [0.65 to 1.29 Gm] daily for over thirteen and a half months, N. P. [case 12] 10 to 15 grains [0.65 to 0.95 Gm] daily for ten months), only J. M. (case 10), who had a marked myotonia of the hands with only moderate atrophy, felt enough improved to desire continuation of the quinine. Her difficulty in walking, however, showed little if any change under quinine therapy. These results are similar to those obtained by Kennedy and Wolf^{3a}. Unlike the patients of Kennedy and Wolf, our patients complained of gastric distress on taking much more than 15 to 20 grains (0.97 to 1.29 Gm) of quinine sulfate a day.

The effect of epinephrine and calcium on myotonia is too evanescent to make these drugs of value for the treatment of myotonia.

ATROPHY

The muscular atrophy is usually the most important disabling feature and at the same time the one least amenable to treatment.

The value of aminoacetic acid in the treatment of progressive muscular dystrophy has been reported by many workers²⁰. Its use in dystrophia myotonica has been limited. Slauck²¹ found no effect from the use of aminoacetic acid by itself but great improvement from aminoacetic acid and testicular extract (see "Testosterone Propionate"). Three patients in this series were given aminoacetic acid over fairly prolonged periods, J. M. (case 10) 30 Gm daily for eight months, N. P. (case 12) about 20 Gm daily for six months, and R. B. (case 8) about 20 Gm daily for one month by itself, for one month with anterior pituitary extract and for two months with testosterone propionate. N. P.

20 Harris, M. M., and Brand, E. Metabolic and Therapeutic Studies in Myopathies, with Special Reference to Glycine Administration, *J. A. M. A.* **101** 1047 (Sept. 30) 1933. Tripoli, C. J., and Beard, H. H. Muscular Dystrophy and Atrophy. Clinical and Biochemical Results Following the Oral Administration of Amino-Acids, *Arch. Int. Med.* **53** 435 (March) 1934.

21 Slauck, A. Die therapeutische Beeinflussbarkeit der Dystrophia myotonica, zugleich ein Beitrag zur Kenntnis vom intermediären Stoffwechsel des Muskels, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, Kong. 45, 1933, p. 175.

(case 12), who believed himself improved with every type of treatment but in whom objective evidences of improvement could not be seen, thought himself improved after administration of aminoacetic acid J M (case 10) at first said that she was improved but near the completion of her period of treatment with aminoacetic acid thought she was no better than she had been at the beginning of the treatment Her husband and many of her neighbors thought she was improved It is quite possible that the progression of the disease was halted Objectively some improvement appeared to occur during the first few months but none during the last months R B (case 8) took aminoacetic acid alone over too short a period to evaluate its effect

Anterior Pituitary Extract—This extract was given because of the widespread nature of the involvement in dystrophia myotonica and the correspondingly large number of regulatory actions which have recently been attributed to the pituitary gland The most striking improvement obtained in any of the patients with any drug was obtained with anterior pituitary extract (Squibb) in J B (case 6) He was given 2 cc of extract three times weekly for a period of about ten months During the first five months he gained 12 pounds (5.4 Kg) in weight, felt stronger and better than he had for years, went out and tried to do some work, no longer had as much difficulty as he had previously in opening doors, and felt happy and encouraged He walked somewhat better than before treatment No change was evident in the myotonia During the last five months of treatment he felt he was no longer gaining, and he stopped the treatment Seen a year after starting treatment, he appeared somewhat better than he had been on starting treatment

N P (case 12) received 2 cc of the drug three times weekly for four months As with all other drugs used, the patient believed himself improved, but objective evidence of improvement was lacking, and during the period of treatment he became conscious of a stiffness of his legs in the morning which he had not noticed previously

R B (case 8) received 2 cc of anterior pituitary extract three times weekly along with 20 to 30 Gm of aminoacetic acid for a month Subjective and objective evidences of improvement were questionable

*Testosterone Propionate*²²—This drug was used for the following reasons

1 Slauck²¹ had reported improvement in the muscular atrophy of dystrophia myotonica by the combined use of aminoacetic acid and a testicular extract (erugon)

2 Testicular atrophy occurred in many of these patients

²² The testosterone propionate used in this study was furnished by the Schering Corporation and the Ciba Pharmaceutical Products, Inc.

3 Papanicolaou and Falk²³ reported that general muscular hypertrophy could be induced in guinea pigs with the androgen

N P (case 12) received 10 mg of testosterone propionate three times weekly for one month and then 25 mg three times weekly for six months. There was no evidence of improvement, and during this period the patient complained of a weakness of the right arm, most evident during shaving. This patient had no testicular atrophy. He said his sexual desire was normal and was not affected by the medication.

O M (case 1) received 25 mg of testosterone propionate twice weekly for six months. The patient, who would probably deny improvement if it did occur, was not sure that he had improved, but his wife thought he was better. That he continued to come for treatment is some evidence, considering his peculiar nature, that he may have been somewhat benefited. His testicles appeared to be atrophic, and he said that he had lost all desire for intercourse and that the testosterone produced no change in his desire, although here again he would probably conceal any change.

R B (case 8) received aminoacetic acid (15 to 30 Gm daily) and testosterone propionate (10 mg daily) for six weeks, then he received testosterone propionate by itself (10 mg daily for one month and 25 mg three times weekly for two months). He was not seen at the conclusion of this treatment, but he thought that he was benefited by the therapy. His sister believes that now, one year after treatment was begun, his hands are stronger than they were previously. The fibrillary twitchings described by Slauck as occurring during administration of the combination of aminoacetic acid and testicular extract and the dramatic improvement which he apparently obtained were not seen in this patient.

F B (case 13) received too few injections of testosterone propionate for him to notice any effect on muscle strength, but he did complain of excessive erections.

Epinephrine and an Epinephrine-Pilocarpine Mixture—Because of the improvement which it produced in the myotonia, epinephrine was given to observe its effect on muscle strength. The epinephrine-pilocarpine mixture (one part of a 1 per cent solution of pilocarpine hydrochloride and two parts of a 1 to 1,000 solution of epinephrine hydrochloride solution) was used because of the improvement which it has been reported to produce in progressive muscle dystrophy²⁴

23 Papanicolaou, G N, and Falk, E A. General Muscular Hypertrophy Induced by Androgenic Hormone, *Science* **87** 238, 1938.

24 Hough, G de N, Jr. Progressive Pseudohypertrophic Muscular Dystrophy. Results of Treatment with Epinephrine and Pilocarpine, *J A M A* **101** 2113 (Dec 30) 1933.

N M (case 2) was given 8 to 11 minims (0.49 to 0.67 cc) of epinephrine subcutaneously twice weekly for four months. She felt benefited, and her family told her that she walked better. Objectively, improvement, although not marked, did appear to be present. She was then given a course of fifty injections of 0.3 cc of the epinephrine-pilocarpine mixture (three times weekly). Again the patient believed that she was definitely improved, and it is true that at the time of writing, over a year after she began the treatment, she appears to be no worse and possibly somewhat improved.

J B (case 6) received several injections of epinephrine and appeared definitely improved. The improvement was especially noticeable in an increased ability to open doors.

Ephedrine Sulfate—J M (case 10) and N P (case 12) both received $\frac{3}{8}$ grain (0.025 Gm) of ephedrine sulfate for several weeks. They were also receiving aminoacetic acid at the same time, and any change due to the ephedrine could not be determined.

Thyroid—O M (case 1) received 5 to 10 grains (0.32 to 0.65 Gm) of thyroid for a period of over two years. He said that he noticed no improvement from it, but according to the records of the physician who gave it to him, the mental and physical lethargy of this patient were markedly decreased by the treatment.

CATARACT

The cataract associated with dystrophia myotonica is adequately treated by operation. The usual type of cataract extraction used in treating patients with senile cataract is also suitable in the treatment of dystrophia myotonica. The operation should be left to the judgment of the surgeon. In our series 1 patient had combined extractions, with a visual result of 20/20 with the proper correcting lens. In another, the extraction was intracapsular, by a modified Verhoeff method, with an equally satisfactory result. No contraindication exists to operation, as there is no evidence of other intraocular pathologic change.

SUMMARY OF TREATMENT

The myotonia can be adequately treated by quinine in these patients, but the quinine does not influence the muscular weakness and atrophy, which produce the greatest disability. Of the many medications used for their effect on the weakness and atrophy, the greatest improvement resulted from anterior pituitary extract in J B (case 6), but anterior pituitary extract produced little if any effect in 2 other patients. Aminoacetic acid, epinephrine and epinephrine with pilocarpine were believed by the patients to have been beneficial, although objective signs of

improvement were not so evident. These drugs may have prevented a progression of the condition. Testosterone propionate was of questionable value. The benefits of ephedrine sulfate cannot be appraised from our limited experience with it. Thyroid has not been given sufficient trial for its effect in overcoming some of the symptoms of hypometabolism which these patients showed.

SUMMARY

A detailed study of 13 patients with dystrophia myotonica is presented. A description of the type of heredity is given, and the conclusion is drawn that the disease is transmitted as a single dominant factor modified by "progressive inheritance." The characteristics of myotonia which distinguish it from simulating conditions are described. The typical pattern of the muscular atrophy is emphasized. The rather typical cataract is believed to be one of the earliest and most constant changes. Various endocrine and metabolic changes which form part of the picture of the disease are described. Mental changes in this group of patients did not appear to be important or characteristic. It is shown in this series, as in some previously reported, that the incidence of cardiovascular changes as indicated by electrocardiographic observations is surprisingly high. Radiologic studies of the gastrointestinal tract revealed nothing of significance. The results of treatment with quinine, aminoacetic acid, anterior pituitary extract, testosterone propionate, epinephrine and epinephrine-pilocarpine mixture and ephedrine sulfate are reported.

Drs L. E. Daniels and J. P. Hilton, of the neurologic service, referred to us J. B. (case 6), N. P. (case 12) and S. B. (case 13), Drs E. A. Schmidt and R. R. Anderson made the fluoroscopic and roentgenographic studies, Dr R. C. Lewis, professor of biochemistry, University of Colorado School of Medicine, and members of his department made the determination of the cholesterol content of the lens removed from N. P. (case 12) and also the many determinations of the blood chemistry and of the basal metabolic rate.

THE FORMATION OF URINE

J GRAHAM EDWARDS, PH D

BUFFALO

The formation of urine is the result of the simultaneous occurrence of three processes, only one of which is explicable in terms of known forces. These processes are (1) glomerular filtration, or the passage of a colloid-free filtrate of blood plasma through the glomerular capillary endothelium and its investing squamous epithelium owing to an excess of hydrostatic over colloid osmotic pressure, (2) tubular excretion, or the passage of solutes from the plasma in the peritubular capillaries through the cells of the proximal convolution of the tubule to its lumen, (3) tubular reabsorption, or the partial removal of solutes and water from the lumen of the distal half of the tubule by its cells (the corrective conservation of certain solids and of water wastefully excreted by the renal corpuscle)

The adequacy of these processes in the indispensable regulation of the composition of the plasma is dependent on the functional integrity of the glomeruli and tubules, as maintained normally by the free passage of blood through the complex glomeruli. Occlusion of the latter (fig 12) or of their arterioles is followed by a breakdown of the vital heterogeneous equilibriums between tissue and fluids in the whole body.

This paper will present a discussion of the formation of urine under normal and under diuretic conditions and of the present knowledge of the chief factors involved. The data of the text and of the figures have been selected with care and in the hope that they are as reliable as is possible at the present time. The text was designed to be separate from the figures so that each might constitute an intelligible unit. The order of presentation is as follows: (1) the structural basis of the formation of urine in man and in other vertebrates, (2) the role of the blood plasma in the formation of urine, (3) glomerular filtration, (4) tubular excretion (secretion) and reabsorption, (5) diuretics, (6) diureses and renal oxygen consumption, (7) conclusions.

THE STRUCTURAL BASIS OF URINE FORMATION

The Renal Unit in Man—There are approximately a million individual structures in the kidney, each composed of a glomerulus, or vascular unit, and a tubule (nephron), or epithelial unit (figs 1 to 4). The vascular unit is significant because of the large surface afforded for the passage from the plasma of water and solutes by its forty to fifty

From the Department of Anatomy, School of Medicine, University of Buffalo

nonanastomosing capillary loops, each about 9 microns in diameter and 0.5 mm in length. Blood enters and leaves these capillaries through an afferent and an efferent arteriole, respectively. These arterioles are otherwise important because, owing to the smooth muscle of their walls

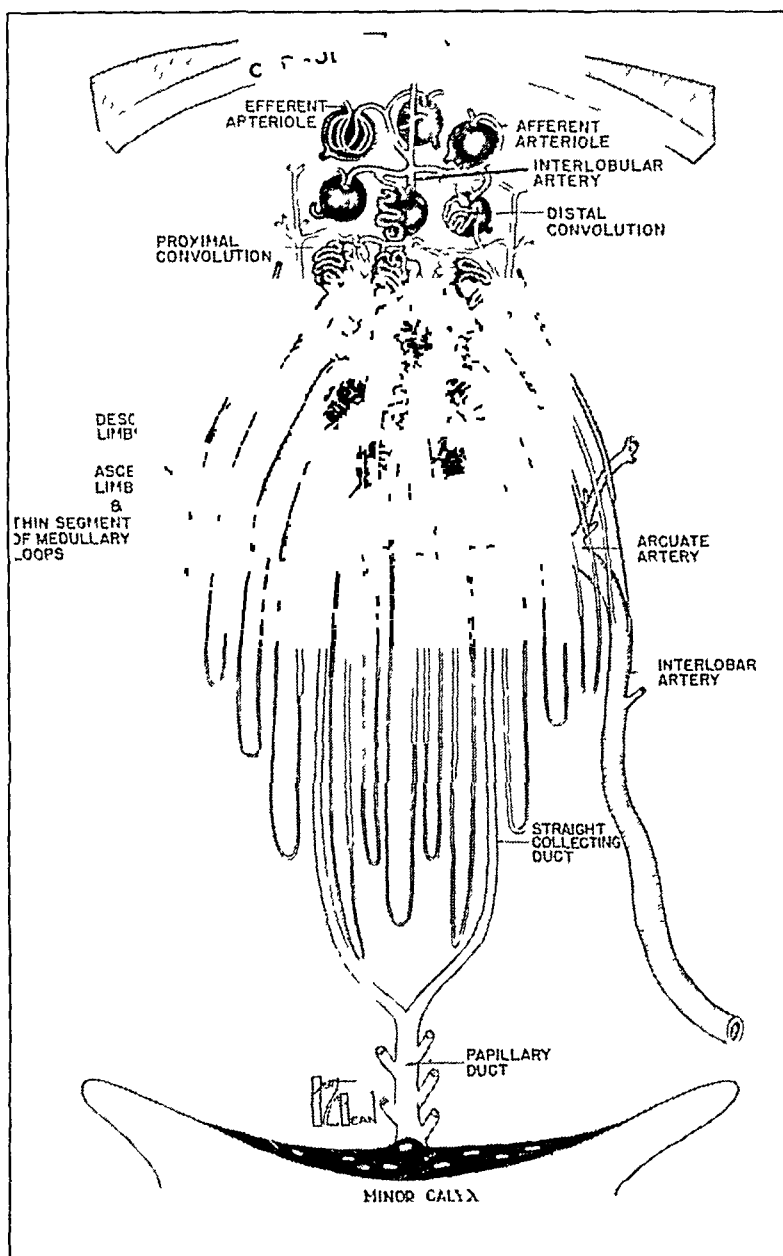


Fig 1—Interlobular renal architecture (Modified and redrawn after Braus, H. *Anatomie des Menschen*, Berlin, Julius Springer, 1924)

and its innervation, they regulate functionally and with marked efficiency the glomerular capillary pressure (see also Goormaghtigh and Handovsky¹). The lumens of both afferent and efferent arterioles near the glomerulus are, under uniform conditions, about 24 microns in diameter

¹ Goormaghtigh, N., and Handovsky, H. Effect of Vitamin D₂ (Calciferol) on the Dog, *Arch Path* 26 1144-1182 (Dec) 1938

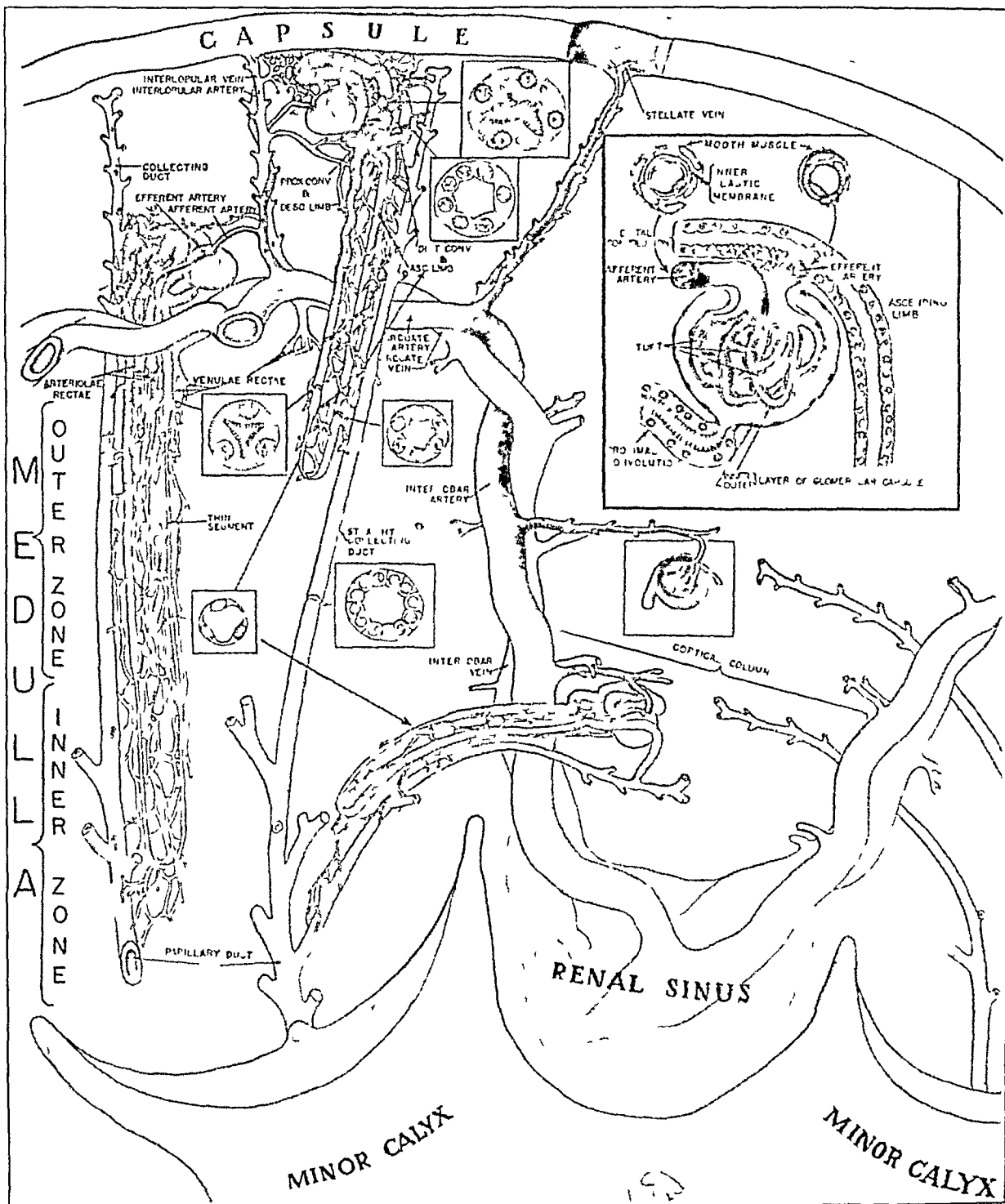


Fig 2—Structure of the human kidney (By the author and self-explanatory, except that in the inset, between and above the afferent and the efferent arteriole, the location of a part of the afferent arteriolar cuff and the epithelial plaque, respectively, should be noted. These were first described by Goormaghtigh [Les segments neuro-myo-arteriels juxta-glomerulaires du rein, *Arch de biol*, Paris **43** 575-591, 1932].)

after fixation Either may vary in size independently of the other as a result of one or more factors which may separately affect their walls or contents

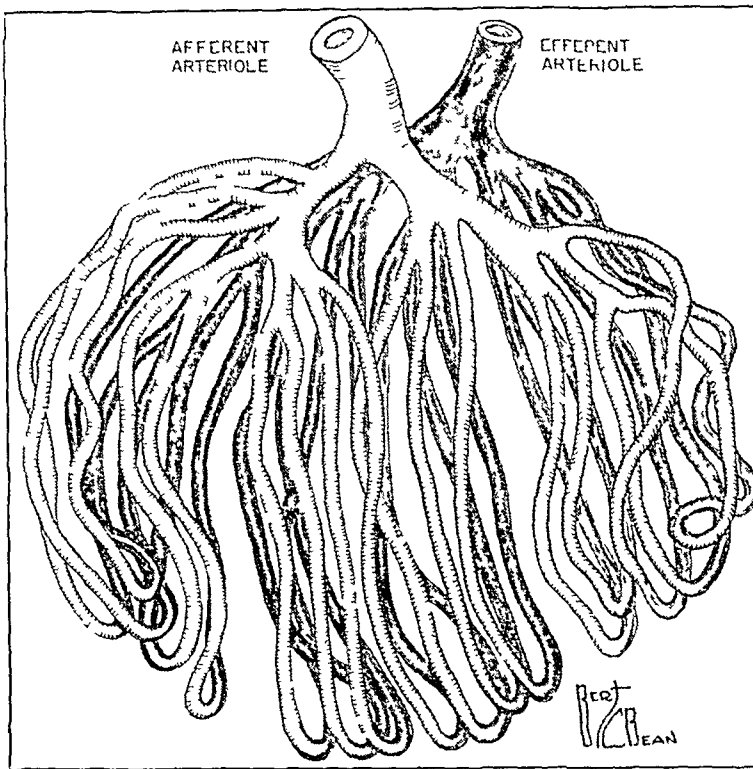


Fig 3—The architecture of the glomerulus (Modified and redrawn after Vimtrup, B On the Number, Shape, Structure and Surface Area of the Glomeruli in the Kidneys of Man and Mammals, *Am J Anat* **41** 123-151 [March] 1928)

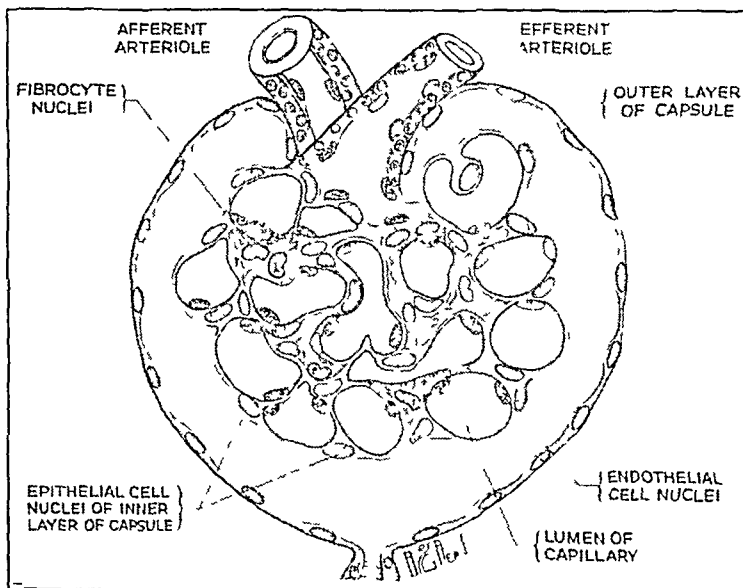


Fig 4—Section of a renal corpuscle (By the author, self-explanatory)

EXPLANATION OF FIGURE 5

The content and concentration relative to plasma of body fluids and the partitions between them, pressures in millimeters of mercury

The sources of the data in the upper section are as follows

Plasma-Lymph Heim, J W On the Chemical Composition of Lymph from Subcutaneous Vessels, *Am J Physiol* **103** 553-558 (March) 1933

Serum-Chest Loeb, R F, Atchley, D W, and Palmer, W W On the Equilibrium Condition Between Blood and Serous Cavity Fluids, *J Gen Physiol* **4** 591-595 (May) 1922

Spinal Fluid Fremont-Smith, F, Dailey, M E., Merritt, H H, Carroll, M P, and Thomas, G W The Equilibrium Between Cerebrospinal Fluid and Blood Plasma, *Arch Neurol & Psychiat* **25** 1271-1289 (June) 1931 Cockrill, J R Nonelectrolytes Their Distribution Between the Blood and the Cerebrospinal Fluid, *ibid* **25** 1297-1306 (June) 1931

Serum-Aqueous Humor (Man) Walker, A M Comparison of the Chemical Composition of Aqueous Humor, Cerebrospinal Fluid, Lymph, Inorganic Phosphate, Uric Acid, Urea, *J Biol Chem* **101** 269-287 (June) 1933 (*Horse*) Duke-Elder, W S XI The Biochemistry of the Aqueous Humor, *Biochem J* **21** 66-77, 1927

Plasma-Glomerular Walker, A M, and Elsom, K A A Quantitative Study of the Glomerular Elimination of Urea in Frogs, *J Biol Chem* **91** 593-616 (May) 1931 Bordley, J, III, Richards, A N, Walker, A M, Reisinger, J A, Westfall, B B, and Findley, T Quantitative Studies of the Composition of Glomerular Urine VIII-XII, *ibid* **101** 193-267 (June) 1933, **107**.661-672 (Dec) 1934 Churchill, E D, Nakazawa, F, and Drinker, C K The Circulation of Body Fluids in the Frog, *J Physiol* **63** 304-308 (Aug) 1927

Plasma-Sweat McSwiney, B A The Composition of the Human Perspiration, *Proc Roy Soc Med* **27** 839-848 (May) 1934

The partitions, lowermost reading down and with stroma and capillary above each partition (first four), are as follows lymphatic capillary endothelium, pleural lining, epithelium of choroid plexus, ciliary epithelium, epithelium surrounding a portion of a glomerular capillary, and a cross section of the secretory portion of a sweat gland

The references for the pressures are as follows


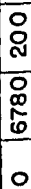



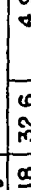
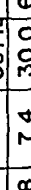



Capillary Blood (Man) Landis, E M Capillary Pressure and Capillary Permeability, *Physiol Rev* **14** 404-481 (July) 1934

Plasma-Colloid Kylin, E Studien uber den kolloidosmotischen Druck im Arterien und Venenblut, *Arch f exper Path u Pharmakol* **159** 401-407, 1931

Capillary Blood and Colloid Osmotic Pressure (Frog) Landis, E M Capillary Pressure and Capillary Permeability, *Physiol Rev* **14** 404-481 (July) 1934

Glomerular Capillary Blood Hayman, J M, Jr Estimations of the Afferent Arteriole and Glomerular Capillary Pressures in the Frog Kidney, *Am J Physiol* **79** 389-409 (Jan) 1927

Intraocular (Man) Adler, F H Clinical Physiology of the Eye, New York, The Macmillan Company, 1933 The capillary blood pressures are approximations The figures 30 + 25 under plasma colloid osmotic pressure represent the colloid osmotic pressure of blood and the intraocular pressure in the anterior chamber of the eye

ANIMAL	FLUID ANALYZED	SPG.	pH	PROTEIN OSPR %	NPN	AMINO ACID MILLIGRAMS PER 100 CG	URIC ACID	CREATININE PER 100 CG	UREA	INORGANIC P	DEXTROSE	NACl	K	CA	PARTITIONS
DOG	PLASMA	1 028	7 4	30 0	618	32 6	4 90	137	217	5 6	123 0	6780	200	117	
	LYMPH	1 015	7 6	12 3	332	348	4 84	140	235	5 9	132 0	711 0	184	984	
MAN	SERUM	1 023		50	380				1200		124 0	6460	130	9 6	
	CHEST	1 009		06	340				1100		1360	6990	6 6	50	
MAN	SERUM	1 028	7 5	72	270		4 72	166	278	3 8	980	5930	209	952	
	SPINAL FLUID	1 005	7 5	003	180		1 67	111	104	1 4	650	7260	147	473	
MAN	SERUM		7 4				3 6		364	3 45	107 7				
	AQUEOUS HUMOR		7 6				2 8		129	1 92	59 7				
HORSE	SERUM			737	240			20	270	30	910	6030	200	106	AS ABOVE
	AQUEOUS HUMOR			002	236			20	280	30	980	6210	180	60	
FROG	PLASMA		77	526	20		404		186	365	660	5050			
	GLOMERULAR		77	0015			407		178	363	643	5130			
MAN	PLASMA	1028	74				60-N	281	260		1000	6000	199	102	
	SWEAT	1003	614				50-N	156	459		126	3700	195	113	

PRESSURES—MM HG

ANIMAL	CAPILLARY BLOOD	CAPILLARY BLOOD PRESSURE	PLASMA COLLOID OS PR	EFFECTIVE FILTRATION & ABSORPTION (-) PR
MAN	ARTERIAL	346	26 6	8 0
	VENOUS	120	23 9	-11 9
FROG	ARTERIAL	10 8	7	3 8
	VENOUS	7 40		0 4
	GLOMERULAR	15 00		8 0
MAN	ARTERIAL INTRAOCULAR	57 00	30 0+25 0*	2 0
	VENOUS INTRAOCULAR	25.00	27 0	-2 0

Figure 5

Since, according to the prevailing conception, most of the renal blood must first pass through the glomeruli before reaching the peritubular capillaries, what occurs during such passage should be considered not as the initial or central aspect in the formation of urine but in relation to subsequent events. It is known, for example, that urinary water is derived from the plasma, chiefly while the latter is passing through the glomerular capillaries. The proteins of this dehydrated plasma normally do not pass in appreciable quantity through the walls of these capillaries. That which prevents their passage is the inner layer of an apical modification of the tubule called the glomerular capsule. (Glomerulus and capsule constitute a renal corpuscle.) This capsule is a two-layered structure, each layer of which is composed of flat epithelial cells. The inner layer, formed by proliferation in fetal life completely invests the glomerular capillaries. Capillary endothelium does not of itself normally prevent the passage of a certain amount of protein (note data for lymph and plasma, fig. 5). In the efferent arteriole and its initial peritubular capillaries the increased concentration of protein in the dehydrated plasma causes an increase in colloid osmotic pressure while the hydrostatic pressure is decreasing or minimal. This situation favors some resorption of the contents of that part of the tubule supplied by these capillaries but may be modified or made ineffective by the intervening cells and other factors.

Another question of interest concerns the existence of numerous renal arteriovenous anastomoses² and the possible effect on the formation of urine of the blood that may be shunted to the tubules without passing through the glomeruli. It is probable that glomerular capillary resistance to blood flow and, especially, the normal serial, temporary cessation of flow through about 25 per cent of the glomeruli³ can so affect renal arterial pressure that arterial blood may pass into anastomotic veins, reverse the flow of incoming capillary blood and reach the peritubular capillaries. This would restore blood volume and raise the pressure in these capillaries, thereby favoring secretion. However, the spatial relations of the two most dynamic and phylogenetically oldest segments of the tubule, i. e., the proximal and distal convolutions (fig. 1), are such that it appears impossible to interpret their disparate function in terms of blood supply or pressure.

The portion of the tubule which leads from the capsule is structurally and functionally the most differentiated. Its correct designation is the proximal convolution with a descending limb. Its cells transport certain of the plasma's constituents directly to the lumen of this portion

² Spanner, R. Ueber Gefasskurzschlusse in der Niere, *Anat. Anz.* (supp.) **85** 81-90, 1938.

³ Hayman, J. M., Jr., and Starr, I., Jr. Experiments on the Glomerular Distribution of Blood in the Mammalian Kidney, *J. Exper. Med.* **42** 641-659 (Nov.) 1925.

and also are probably active in the synthesis of substances other than the ammonia and hippuric acid known to be formed in the kidney. The upper part of the descending limb leads abruptly into a straight, more deeply medullary portion of variable length, which, because of its small diameter, is called the thin segment. The thin segment attains its highest development in mammals. Its cells are flat, although not so flat as those of the capsule, the lumen, therefore, constitutes most of its diameter and

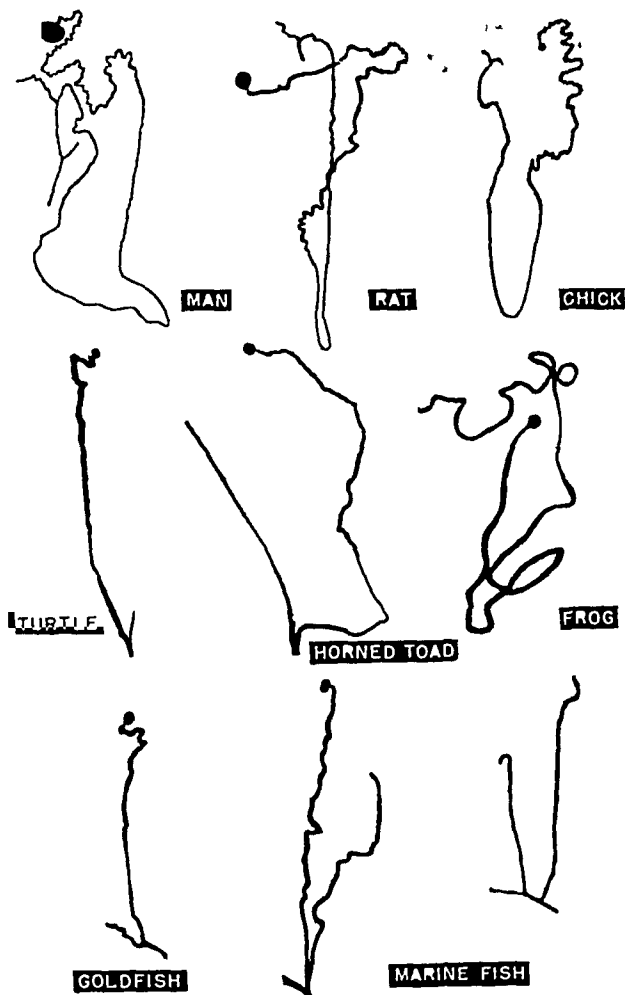


Fig 6—Photomicrographs of renal units isolated by the author. Note the two tubules constituting the lower center figure, the one long and glomerular and the other short and aglomerular. These two types are present in the same kidney and presumably are simultaneously functional. At the lower right are shown two aglomerular tubules from a kidney totally lacking glomeruli.

is about as large as that of the adjacent, thick portions. It is claimed that some of the water in the lumen of this segment passes through its cells to the peritubular blood.⁴

⁴ Gersh, I, and Stieglitz, E. J. Histochemical Studies on the Mammalian Kidney. I. The Glomerular Elimination of Ferrocyanide in the Rabbit and Some Related Problems, *Anat Rec* 58 349-367 (March 25) 1934.

The thin segment is also sharply demarcated from the ascending limb. This limb extends, parallel with the descending limb, from various levels in the medulla to its glomerulus in the cortex (fig 1). Here it or the initial portion of the distal convolution is attached by an elliptic plaque of narrow columnar cells to the vascular pole of the corpuscle⁵ and is succeeded by the coiled distal convolution proper. Its cells are primarily active in the resorption of water, while those of the distal convolution are similarly active in the resorption of solutes⁶. In the frog and the rat it is in the lumen of the middle third of the distal convolution that the p_H of the fluid, hitherto the same as that of plasma, drops as a result of the resorption of base, or its equivalent⁷.

In addition to the structurally different parts of the tubule, there is good evidence that in the proximal and distal convolutions there are several functionally discrete segments which have not been histologically recognized. In the kidneys of the cat and dog the presence of fatlike globules or vacuoles in certain cells of the proximal convolution and apparent changes in the contour of cell boundaries might properly be regarded as more indicative of functional than of structural specificity. Other indications of such specificity in this convolution are seen in human and other mammalian kidneys. For example, by the use of suitable methods iron is normally demonstrable in the cells of 2 to 3 mm of the third quarter of the proximal convolution. After the introduction of large amounts of urea into the dog⁸ or the rat (the only animals studied) the cells of 2 to 3 mm of the second quarter of the convolution are definitely affected (fig 9). Also, in chronic nephritis and

5 Goormaghtigh, N. L'appareil neuro-myo-arteriel juxta-glomerulaire du rein, ses réactions en pathologie et ses rapports avec le tube urinaire, *Compt rend Soc de biol* **124** 293-296, 1937.

6 (a) Okkels, H. Differences entre les diverses cellules du troisième segment du tube urinaire chez les vertebres, *Bull d'histol appliq à la physiol* **6** 12-33 (Jan) 1929. (b) Edwards, J. G. Functional Sites and Morphological Differentiation in the Renal Tubule, *Anat Rec* **55** 343-367 (March 25) 1933. (c) Feyel, P. Sur l'existence et le rôle de cellules spéciales dans le segment intermédiaire et le tube de Bellini du rein chez la souris, *Compt rend Soc de biol* **115** 1148-1151, 1934. (d) Walker, A. M., Hudson, C. L., Findley, T., Jr., and Richards, A. N. The Total Molecular Concentration and the Chloride Concentration of Fluid from Different Segments of the Renal Tubule of Amphibia, *Am J Physiol* **118** 121-129 (Jan) 1937.

7 (a) Montgomery, H., and Pierce, J. A. The Site of the Acidification of the Urine Within the Renal Tubule in Amphibia, *Am J Physiol* **118** 144-152 (Jan) 1937. (b) Edwards, J. G. Demonstrable Functions of the Renal Tubule After It Has Been Segmentally Injured by the Action of Mercuric Chloride, *ibid* **119** 302 (June) 1937.

8 Hartman, F. W. Methods and Effects of Increasing the Urinary Constituents in the Body, *J Exper Med* **58** 649-662 (Dec) 1933.

after mercurial poisoning marked changes (compensatory hypertrophy⁹ and injury,^{7b} respectively) occur in segments of this convolution, with which is associated a diminution of the renal phosphatase content¹⁰

These structural and functional indications that each part of the tubule is in some specific way active in the formation of urine suggests two

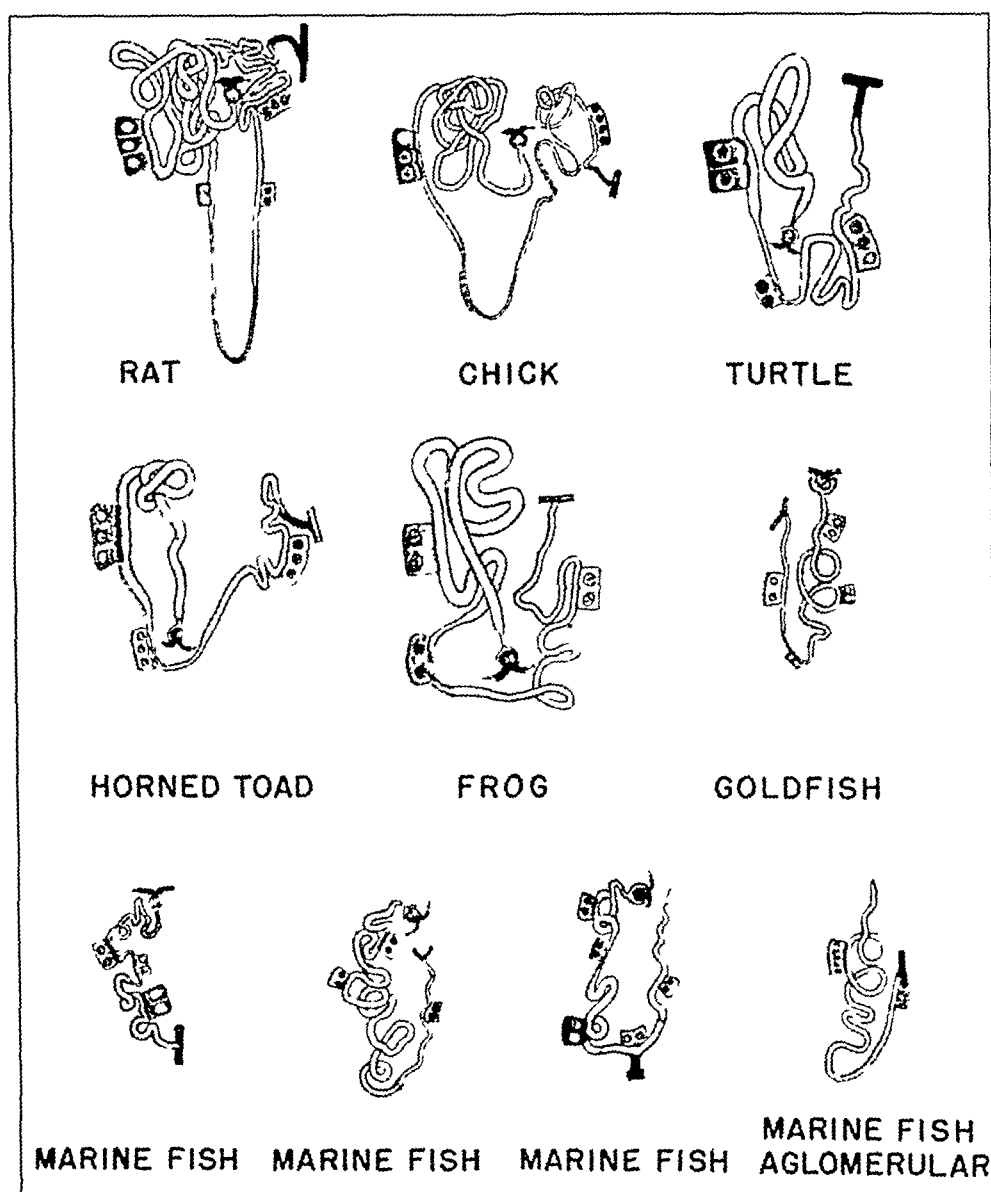


Fig 7—Diagrams of various renal units with insets which indicate something of the character of the epithelium of the units' component segments

queries 1 How do the cells of these parts in transporting water and solutes to and from the lumen of the tubule and peritubular capillaries

9 Oliver, J, and Luey, A S The Morphology of the Abnormal Nephron in Terminal Hemorrhagic Bright's Disease, Arch Path **18**:777-816 (Dec) 1934

10 Brain, R T, and Kay, H D Kidney Phosphatase Enzyme in Disease, Biochem J **21**:1104-1108, 1927

overcome osmotic or other resistance such as should, to some extent at least, exist between luminal, cellular, interstitial and capillary fluids?

2 How do cells in one portion of the distal convolution which are seemingly identical in structure with those in an adjacent portion constitute a segment so specific in its selection of substance to be resorbed that the p_H of the luminal fluid of this segment is changed?

The Renal Unit in Other Vertebrates—Figures 6 and 7 show various renal units. The simplest unit is a coiled tubule which, throughout its length, is structurally similar to the proximal convolution in the kidney of all classes of vertebrates. This is the aglomerular tubule. The kidneys of certain fish contain tubules solely of this type and excrete urine whose constituents are like those of the urine of vertebrates in general (fig. 8).

	CERTAIN FISH <i>Non- or Aglomerular Mesonephros</i>		FROG <i>Glomerular Mesonephros</i>		TURTLE <i>Glomerular Metanephros</i>		BIRD <i>Glomerular Metanephros</i>		RAT <i>Glomerular Metanephros</i>		HUMAN <i>Glomerular Metanephros</i>	
CONSTITUENT	BLOOD	URINE	BLOOD	URINE	SERUM	URINE	PLASMA	URINE	PLASMA	URINE	PLASMA	URINE
Nonprotein N	520	1970	1313	784	660	4000		1000	450	773.5	310	11200
Urea	560	350	214	1391	384	1070		22.3	404	1258.3	300	20810
Uric Acid	0.84	17	0.7	0.12	0.5	40.4	6.0	1970		13.3	2.0	600
Ammonia	6.8	447		46		43.2		210		969	1.0	59.5
Creatine	4.47	2684	16	43	48	20.5	5.0	140		934	5.0	
Creatinine	1.49	42.6	2.3	2.9	1.7	9.2	1.3	40	0.6	484	1.5	107.7
Undetermined N			1.5	70	30.5	66.5		14		48.8	9.3	38.4
Sodium	5560	1880		111			2650	940			3000	3500
Chloride	6460	4470	2750	380	2630	130	4150	1460	3120	1340	3750	5000
Potassium	250	100		7.5							200	1370
Calcium	105	600		170	920	600		281.6			100	150
Magnesium	110	1790		0.3							30	60
Phosphorus	25.2	54	5.3	6.9	66	51.6	4.0	360	67	64.6	30	1500

Fig. 8—Analysis of the blood and urine of vertebrates, expressed in milligrams per hundred cubic centimeters. The figures are original data of the author's except the analyses of the blood and urine of the fowl and man, for the acknowledgment of which see Edwards, J. G., and Condorelli, L. *Am. J. Physiol.* **86**: 383-398 (Sept.) 1928.

The glomerular renal unit is generally composed of (1) a corpuscle (fig. 4), (2) a neck segment, which in cold-blooded animals is short, narrow and usually ciliated but in warm-blooded animals is merely a sharp transition from the squamous epithelium of the corpuscle to the columnar epithelium of the next segment, (3) a proximal convolution composed of acid-staining, brush-bordered cells, which constitutes the longest subdivision of the tubule, (4) in cold-blooded animals an intermediate segment, which is usually interposed between the proximal and the distal convolution and which averages 0.2 mm. in length, or, in warm-blooded animals, a thin segment, 1 to 10 mm. long, which occupies

a similar locus in the tubule, (5) a succeeding distal convolution, composed of light-staining, more or less cuboidal cells (in the mammalian and to some extent in the avian kidney it is preceded by an ascending limb composed of similar cells)

The renal tubule of marine fish differs in one major respect from that of fresh water fish and other vertebrates—it lacks a distal convolution

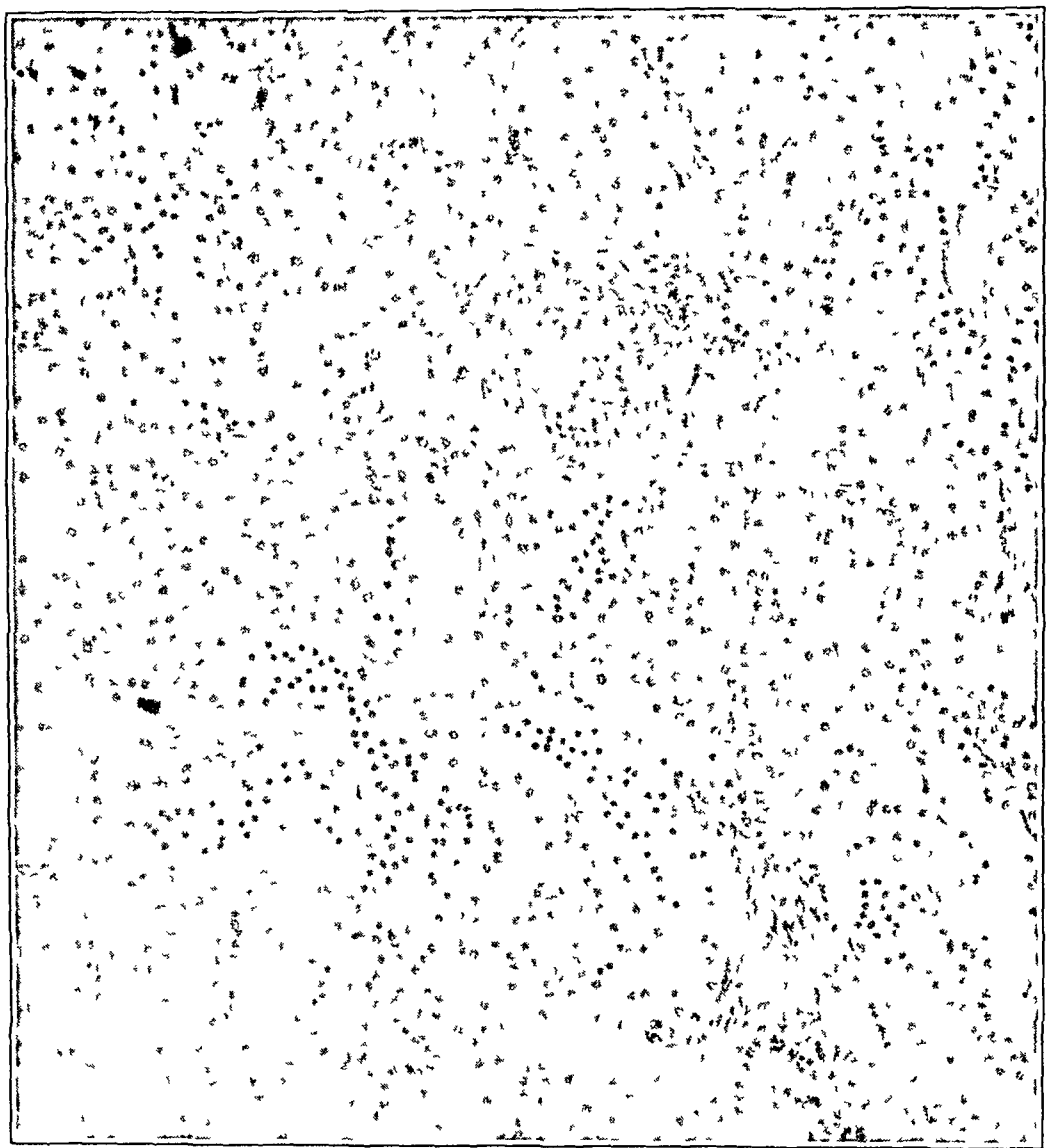


Fig 9—The segmental effect on the proximal convolution (light-staining portions) of the tubule in the rat's kidney following repeated intraperitoneal injections of 5 cc of a 20 per cent solution of urea

However, the urine of these fish and that of other vertebrates are comparable (fig 8). In marine and in fresh water fish the tubules, or proximal convolutions, are multisegmental and bisegmental, respectively, regardless of the relatively insignificant glomerular development in marine fish. The glomerular tubule is structurally more differentiated and is of greater length than the aglomerular tubule.

The *proximal* convolution is the only part of the renal unit that is invariably present in the kidney of all classes of vertebrates. This fact, and others pertaining to the tubule in general, seem to warrant inclusion of the data¹¹ given in the following tabulation and in the succeeding paragraphs and tabulations.

Subject and Age	Renal Mass, Cc	Number Glomeruli per Given Renal Mass	Diameter, Microns	
			Glomeruli	Proximal Convolution
Premature birth	6.5	122	85	
Girl, 1	21.0	46	88	38
Girl, 4	55.0	18	150	53
Girl, 5	60.0	17	149	51
Girl, 18	115.0	11	190	54
Man, 32	120.0	10	213	55
Man, 40	130.0	11	195	53
Woman, 46	120.0	9	196	65

The number of glomeruli per cubic millimeter of renal cortex in man and the pig is 4 to 6, in the rat and the guinea pig, 15, in the crow, 90 to 100, in the duck, 230 to 300, in the weaver bird, 400 to 450. These data indicate the relative space occupied by glomeruli and tubules in mammals and birds.

Measurements of various renal units are given in the following tabulation in order to show, comparatively, the diameter in microns of the glomerulus, G, or vascular unit, the length in millimeters of the proximal convolution, PC, or secretory unit, the length of the thin segment, TS, ascending limb, AL, and distal convolution, DC, which collectively are to be regarded as the resorptive unit. The total length of the tubule, TL, is also given.

	G	PC	TS	AL	DC	TS+AL	AL+DC	TS+AL +DC	TL
Man	200	14	6	9	4.6	15.0	13.6	19.6	33.6
Ox	190	19	12	10	1.3	22.0	11.3	23.3	42.3
Pig	240	19	5	5	2.5	10.0	7.5	12.5	31.5
Sheep	180	16	8	7	2.0	15.0	9.0	17.0	33.0
Rabbit	110	7	6	4.5	0.8	10.5	5.3	11.3	18.3
Cat	124	9	8	6	1.2	14.0	7.2	15.2	24.2
Rat	100	11	5	8	1.5	13.0	9.5	14.5	25.5
Mouse	80	3	2	1.5	0.7	3.5	2.2	4.2	7.2
Porpoise	130	5	4	2.5	1.3	6.5	3.8	7.8	12.8
Chick	40	6	1.5	3.5	4.0	5.0	7.5	9.0	14.0
Turtle	50	2	0.2		1.4			1.6	3.6
Frog	100	3.8	0.2		3.0			3.2	7.0
Goldfish	60	2	0.2		1.5			1.7	3.7
Marine fish									
Glom	30.90	5							5.0
Aglom		3							3.0

Because, in general, in all classes of vertebrates, solutes and some water are transported from peritubular capillaries to the lumen of the proximal convolution, and (except in marine fish) water and solutes are transported from the lumen to peritubular fluid or capillary blood in the remainder of the tubule, the tubule is divisible functionally into a mini-

¹¹ von Mollendorff, W. Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 1, pp. 1-374.

sum of two segments—namely, a proximal convolution or secretory unit and a distal convolution or resorptive unit. In the foregoing data the lengths of these two segments are given in black letter type (PC, the length of the proximal convolution, and TS + AL + DC, the sum of the lengths of the remaining portions of the tubule). It is noteworthy that the length of the proximal convolution in mammals and in the chick is less than the sum of the lengths of the remaining portions, while the

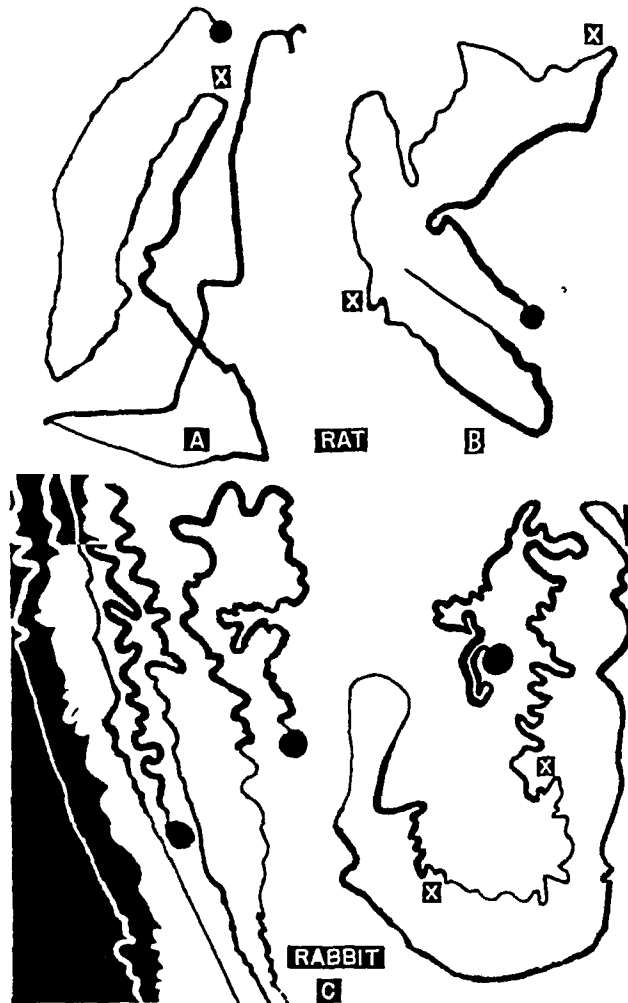


Fig 10—Photomicrographs of renal units isolated by the author showing the extent and segmental character of the lesions in the proximal convolution induced by mercury under various conditions. In *A*, from the glomerulus (knob) at top to *X*, in *B* and *C*, right, *X* to *X*, and in *C*, left, narrow portions except for the thin segment (normal) in the lower part of the third tubule from the left.

opposite is true in cold-blooded animals. The different lengths of the resorptive portions probably constitute the basis for the fact that mammalian urine is normally hypertonic, that of the chick, hypertonic or isotonic, and that of the cold-blooded animals, definitely hypotonic.¹²

¹² Edwards, J. G., and Condorelli, L. Studies on Agglomerular and Glomerular Kidneys. II. Physiological, *Am J Physiol* 86: 383-398 (Sept.) 1928.

BLOOD PLASMA AND URINE FORMATION

Blood plasma is the immediate source of body fluids. Their composition relative to plasma (fig 5) indicates that some are filtrates. Filtrates are colloid free but are otherwise identical in composition with the



Fig 11—Photomicrographs of a rabbit's kidney. *A* shows well preserved upper portions of proximal convolutions and two renal corpuscles whose outlet to the tubule has become occluded by connective tissue within three months after the injection of 10 mg of mercury. In *B* is shown the character of the lesion observable in 2 mm of the lower third of the proximal convolution in the kidney of the same animal.

plasma, from which they are derived as the result of an excess of hydrostatic over colloid osmotic pressure in the blood capillaries. That fluids derived from plasma may differ significantly from it in composition or in concentration is attributable to the character of the epithelial partitions

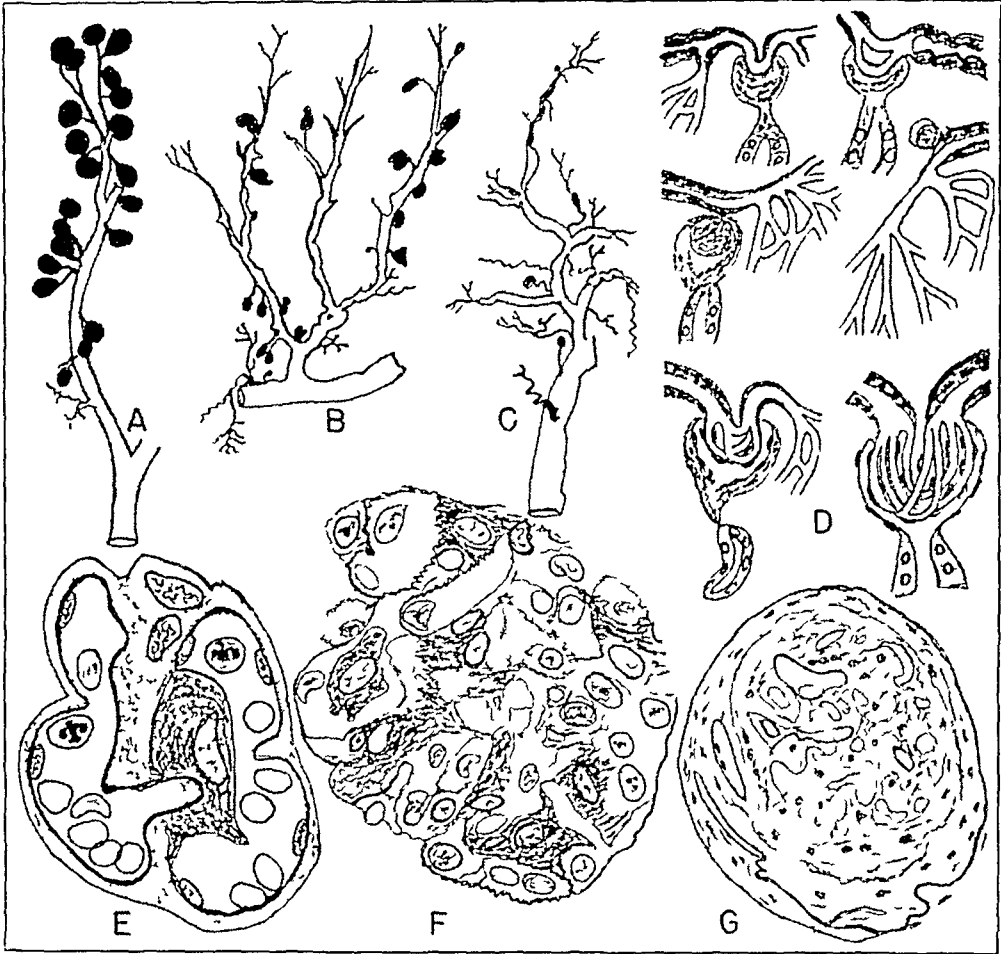


Fig 12 —Diagrams of various stages in glomerular degeneration. In *A*, *B* and *C* is indicated the decrease in number of glomeruli (solid black) occurring in chronic arteriosclerotic nephritis. In *D*, top, left, is shown a preglomerular branch of an efferent arteriole, a looped shunt remaining after occlusion of the other glomerular capillaries, and the efferent arteriole with bifurcated termination. In *D*, top, right, is shown a two-looped shunt between afferent (right) and efferent arterioles. The two middle diagrams in *D* represent a continuation of afferent and efferent arterioles, with marked atrophy of the slightly attached glomeruli. The two lower diagrams illustrate, left, an earlier stage in the glomerular atrophy, right, a normal glomerulus. In *E*, *F* and *G* are shown stages in the development of glomerular, intercapillary connective tissue resulting in occlusion of the capillaries and atrophy of the glomerulus (*A*, *B* and *C*, after Loomis, *D* Plastic Studies in Abnormal Renal Architecture. IV Vascular and Parenchymal Changes in Arteriosclerotic Bright's Disease, Arch Path 22 435-463 [Oct] 1936. *D*, six schematic diagrams by the author, based on the cited work of Loomis. *E* and *F*, after Bell, E. T. A Text-Book of Pathology ed 3, Philadelphia, Lea & Febiger, 1928. *G*, after MacCallum, W. G. A Text-Book of Pathology, ed 6, Philadelphia, W. B. Saunders Company, 1936.)

through which they pass¹³ Squamous cells are present at the site of the formation of approximate filtriates (in fig 5, under "Partitions," note the lymphatic endothelium and the epithelial investment of a glomerular capillary) Also, in the development of the mammalian kidney, the epithelium of the inner layer of the glomerular capsule does not appear to function until it has become adequately squamous¹⁴

Several factors suggest that the fluid in the glomerular capsule is a filtrate For example, when the intracapsular pressure equals the effective filtration pressure (glomerular capillary pressure in excess of colloid osmotic pressure) formation of an appreciable amount of intracapsular fluid generally stops, likewise, such formation ceases when the hydrostatic capillary pressure equals the plasma colloid osmotic pressure The fluid in the glomerular capsule of cold-blooded animals is approximately a plasma filtrate Data on the frog are given in table 1 Independent confirmation of the analysis of this filtrate is unfortunately lacking There is, nevertheless, considerable evidence that filtration is responsible for the presence of the intracapsular fluid and, as such, constitutes an important aspect of urine formation However, this fluid should not be referred to as glomerular or provisional urine because a plasma filtrate is not urine Urine formation begins, continues and ends in the tubule, regardless of whether urinary constituents are immediately derived from intracapsular or from peritubular fluid The processes involved in urine formation are commonly designated as filtration, secretion and resorption, but the formation of a plasma filtrate has nothing to do with its subsequent differentiation

Recent studies of the kidneys of mammalian fetuses and of developing chicks show that the cells of the proximal convolution become functional before those of the glomerular capsule¹⁴ Just what functional changes may be initiated in the cells of this convolution or in the tubule as a whole, after the requisite flattening of the inner layer of the capsule and the coincident formation of intracapsular fluid, are at present entirely speculative I¹⁵ have called attention to structural and probable functional changes in the tubule contingent on its attachment to a glomerulus

I conceive of urine formation as proceeding simultaneously in the several parts of the tubule, accompanied by the formation of an intracapsular filtrate During the passage of the latter through the tubule,

13 Flexner, L B, and Stiehler, R D Biochemical Changes Associated with the Onset of Secretion in the Fetal Choroid Plexus An Organization of Oxidation-Reduction Processes, *J Biol Chem* **126** 619-626 (Dec) 1938

14 Gersh, I The Correlation of Structure and Function in the Developing Mesonephros and Metanephros, Publication 479, Carnegie Institution of Washington, 1937, *Contrib Embryol* (no 153) **26** 33-58 (Jan) 1937

15 Edwards, J G The Epithelium of the Renal Tubule in Bony Fish, *Anat Rec* **63** 263-279 (Oct 25) 1935

some of it is resorbed and the remainder becomes urine (Other filtrates, comparable except for their content of protein or a difference in the concentration of their constituents relative to plasma, become such fluids as interstitial fluid or lymph, aqueous humor, cerebrospinal fluid and endolymph) Fractions of the filtrable plasma pass simultaneously into the lumen of the tubule via the corpuscle and the cells of the proximal convolution, to be returned in part to peritubular fluid or capillary blood by the cells of the remaining portions of the tubule There is no valid proof as yet that any constituent normally present in the urine arrives there from the plasma solely by passage through the renal corpuscle

It is interesting that in the frog the dextrose which enters the tubule from the glomerular capsule gradually disappears during its passage through the lumen of the proximal convolution, while at the same time and in the same area the concentration of urea increases¹⁶ In other vertebrates (fish, an amphibian, the chick, anthropoid ape and man) it is presumed that dextrose disappears as the creatinine increases¹⁷ (comparably with urea in the frog) It is demonstrable that in the kidneys of diabetic persons glycogen is deposited in the cells of a segment of the proximal convolution When the cells of the latter are poisoned by the glucoside phlorhizin, dextrose is copiously excreted, but there is little or no change in the quantitative excretion of other urinary constituents A somewhat similar situation obtains when a portion of this convolution is affected by mercury Despite evidence that dextrose is resorbed by the cells of the proximal convolution, the possibility still remains that, instead of a direct transfer of this substance to peritubular capillaries, something quite different occurs

All of the more pertinent and reliable data indicate that the concentration of the fluid in the lumen of the proximal convolution progressively increases as a result of the addition of solutes and possibly of the resorption of a small amount of water This progressive concentration continues more rapidly in the next two segments of the tubule as a result of the resorption of a relatively large amount of water In the distal convolution, solutes are resorbed¹⁸ The speed of resorption by the cells of a segment of this convolution in the frog's kidney has been shown by perfusing a single tubule with a 0.33 molar solution of sodium phosphate (p_H 7.5) The p_H of the luminal fluid shifted from 7.5 to 6.8 in one minute^{7a} It seems probable that the fluid in the lumen of the tubule is

16 Walker, A. M., and Hudson, C. L. The Reabsorption of Glucose from the Renal Tubule in Amphibia and the Action of Phlorhizin upon It, *Am J Physiol* **118** 130-143 (Jan) 1937

17 Smith, H. W. The Physiology of the Kidney, New York, Oxford University Press, 1937, pp 1-310

18 Gersh and Stieglitz⁴ Walker and others^{6d} Edwards^{7b} Gersh¹⁴

never in osmotic equilibrium with plasma, although it may be in such equilibrium with peritubular fluid. Therefore, the additions to this fluid and subtractions from it are made against osmotic gradients.

GLOMERULAR FILTRATION

Commendable efforts have been made during the past few years to measure glomerular filtration, despite the failure of Rehberg and others in this connection. A substance has been sought¹⁹ which, without disturbing normal processes, would be excreted solely by filtration, without subsequent resorption. Some investigators are now convinced that the polysaccharide inulin is such a substance. If so, therefore, a reliable method is available for measuring glomerular filtration, for determining whether a given urinary constituent is excreted by filtration alone or by filtration and tubular excretion and for estimating the degree of resorption of the constituent and of water. If a substance is filtered—that is, excreted—entirely via the corpuscle, the degree of its concentration in the urine will show the amount of water resorbed. The amount of inulin excreted in the urine in one minute (rate of excretion) divided by the amount contained in 1 cc of plasma gives the volume of glomerular filtrate in cubic centimeters per minute (rate of filtration). When two or more substances, under a variety of conditions, are simultaneously excreted at rates identical in relation to their respective concentrations in the plasma it is claimed that such substances are excreted solely by filtration, without resorption. Further, if the plasma concentration of a substance which is eliminated in part by the cells of the tubule (creatinine is said to be such a substance) is raised variably above its normal level, the amount eliminated can be reduced until it approaches that supplied by glomerular filtration alone.

Without stating the details of the results obtained by several investigators in studies of the mode of excretion of certain foreign and normal substances, the possibilities inherent in such excretion may be summarized as follows:

1 If a substance is excreted by filtration but is partially resorbed, the rate of its excretion will be *less* than the rate of filtration.

2 If a substance is excreted by filtration and by the tubule but is not resorbed, the rate of its excretion will be *greater* than the rate of filtration.

3 When a substance is excreted by filtration and by the tubule, if an amount is then resorbed equal to the amount excreted by filtration or by the tubule, the rate of excretion will be equal to the rate of tubular excretion or of glomerular filtration, respectively.

¹⁹ Jolliffe, N., Shannon, J. A., and Smith, H. W. The Excretion of Urine in the Dog. III. The Use of Non-Metabolized Sugars in the Measurement of the Glomerular Filtrate, *Am J Physiol* **100** 301-312 (April) 1932.

4 A substance may be excreted partly by filtration and partly by tubular excretion and may then be partially resorbed in such amounts that the rate of excretion is invariably less than the rate of glomerular filtration

Whatever may be the mode of excretion of inulin, I am of the opinion that the precise mode of excretion of any normal urinary constituent has not been determined by the use of this substance

TUBULAR EXCRETION

This discussion of tubular excretion is based on data compiled by Smith¹⁷ Just as inulin, a substance foreign to blood plasma, appears to be excreted by filtration alone, so another substance, phenolsulfonphthalein (phenol red), also foreign to the plasma, appears to be almost if not as completely excreted by the proximal convolution of the tubule, without being resorbed Of the amount of phenolsulfonphthalein administered 94 per cent is excreted by the tubule Since I have found that some of the dye is destroyed in the body or eliminated in the feces, the foregoing percentage may represent its total excretion in the urine The rate of its excretion when the plasma contains 0.1 to 1.0 mg per hundred cubic centimeters is much greater than that of inulin, although at such concentrations 80 per cent of the dye is bound to the albumin fraction of the plasma proteins The rate of excretion is independent of the rate of urine formation and does not increase in direct proportion to the concentration of phenolsulfonphthalein in the plasma Instead, as the concentration of phenolsulfonphthalein in the plasma is increased from 1 to 20 mg or more per hundred cubic centimeters its excretion by the tubule is progressively decreased and, despite the increase in the amount of free dye at higher concentrations, the total excretion is reduced Such behavior is said to be characteristic of substances excreted by the tubule, regardless of their filtrability, but not of those excreted by the corpuscle Verne²⁰ noted similar excretory activity in the aglomerular kidney

Several organic compounds of iodine are also excreted by the tubule with remarkable efficiency²¹ With regard to one of them (diodrast) it is said²² that its excretion measures the effective renal blood flow (the volume of blood supplied to the secretory portion of the tubule), since this excretion is limited normally by blood flow but not, within a wide

20 Verne, J Contribution à l'étude des reins agglomérulaires, l'appareil renal des poissons lophobranches, Arch d'anat micr **18**:357-407, 1922

21 Landis, E M, Elsom, K A, Bott, P A, and Shiels, E H Simultaneous Plasma Clearances of Creatinine and Certain Organic Compounds of Iodine in Relation to Human Kidney Function, J Clin Investigation **15** 397-410 (July) 1936

22 Shannon, J A Renal Tubular Excretion, Physiol Rev **19** 63-93 (Jan) 1939

range, by the amount of the substance in the blood or by the excretory capacity of the tubule. Excretion of phenolsulfonphthalein, however, is limited by the amount of secretory tissue but is not correlated with blood flow or the concentration of the dye in the plasma.

Thus it follows, and is of clinical interest, that the excretion of inulin may be used as a measure of glomerular filtration, that of diodrast may be used as a measure (*a*) of renal blood flow and (*b*) (in conjunction with phenolsulfonphthalein or dextrose) of the amount of renal secretory tissue and of the functional state (normal or damaged) of the proximal convolution. However, such use of diodrast is still more a hope than a realization.

The preferred excretion of certain substances (inulin, sodium ferrocyanide) by the corpuscle and of others (iodine compounds) by the cells of the proximal convolution when all of them are completely filtrable—that is, they are not bound to plasma protein or of such molecular size as to limit their passage through the corpuscle—shows that filtrability cannot be a factor in their respective modes of excretion. That the excretion of iodine compounds by the cells of the proximal convolution is more efficient than that of inulin by the corpuscle is evidence of the excretory potency of this part of the tubule. This potency, together with the comparatively great size and length of the convolution in mammals and other vertebrates, especially in compensatory hypertrophy, should cause reluctance to accept such evidence as now seems to indicate, or is interpreted to indicate, that most urinary constituents are excreted by the corpuscle. The excretion of inulin may measure glomerular filtration, but, despite coincidences suggestive of a similar mode of excretion of other substances, it does not follow as yet that inulin can be reliably used to indicate the mode of excretion of normal urinary constituents.

Phylogenetically and actually, the tubule is responsible for the character of urine, but this does not mean that selective and partial resorption of a glomerular filtrate is the chief task which the tubule is normally required to perform, or that the initial and central feature in urine formation is glomerular filtration. For, while the urine in extreme diuresis approaches a plasma filtrate in the concentration of its constituents, a diuretic type of urine is excreted also by kidneys lacking glomeruli and distal convolutions.²³ There is no reason to give precedence to glomerular filtration over the other processes of urine formation. All three processes in the adult kidney are simultaneous and mutually interrelated, although developmentally the tubule is excretory before the corpuscle. In the urine-forming activity of the tubule, in both the aglomerular and the glomerular kidney, blood pressure is an incidental factor. In the

23 Bieter, R. N. Further Studies Concerning the Action of Diuretics upon the Aglomerular Kidney, *J. Pharmacol. & Exper. Therap.* **49** 250-256 (Oct.) 1933

filtrate-forming activity of the corpuscle, however, blood pressure is the major factor. These circumstances and others should be considered in the study of the total complex of the formation of urine.

DIURETICS

Substances inducing an increase in urine volume are definable as diuretics. Their use thus far has not revealed new factors in urine formation or renal function but has variably illustrated all the known factors. Abnormal increase or change in the percentage composition of the constituents of blood plasma is usually followed by a diuresis in which solutes are reduced in percentage but may be increased in total amount. Such diureses restore or tend to restore the normal composition, p_H , volume or osmotic pressure of plasma. This emphasizes the nature of normal as well as of heightened renal function and is reflected in the composition or in the volume of the urine.

The cations of the fixed bases, sodium and potassium, are excreted with considerable water when present in excess in plasma. Sodium, the predominant base in extracellular fluid, and potassium, that in intracellular fluid, are excreted (or retained) after changes affecting these fluids. These ions seem functionally different in general metabolism and in their action on the cells of the renal tubule. One indication of this difference is seen in adrenal insufficiency, in which excretion of sodium chloride and water is increased, while in the plasma potassium is increased and sodium chloride decreased. The relative immobility of potassium and its unfavorable effect on the sodium balance appear to constitute the basis for the behavior of the two ions under normal conditions and under those of diuresis and edema.

The ingestion or injection of the chlorides of ammonium, calcium and magnesium causes an increase of chloride in the plasma, a reduction of bicarbonate and a lowering of p_H and osmotic pressure. The attendant diuresis is marked by the excretion of water and fixed base and/or ammonia of renal origin.

Dextrose, urea and sodium chloride act as diuretics because, in addition to their effects on the plasma, their increased excretion limits the resorption of water from the lumen of the tubule. Such diureses are called "tubule" or osmotic diureses, in contradistinction to the "dilution" diureses attributable to excessive filtration without compensatory resorption. All diureses are the result of some antecedent changes which may affect singly or in combination the blood plasma and the cardiovascular, renal vascular and tubular systems. Salts, dextrose and urea are examples of "tubule" diuretics. It is probable that most diureses are, in considerable part, the result of increased filtration, which causes more of fluid to pass through the tubule than can be resorbed or of the osmotic resistance to water resorption caused by the increased excretion of solutes. The

methyl purines, such as caffeine, seem to affect all of the systems mentioned, and therefore the urine may show the variable effects of changes in these systems

Mercurials, mercupurin and acidifying salts cause (*a*) changes in the blood plasma, which bring about marked increase in the excretion of chloride, (*b*) changes in the glomeruli, which result in an increased filtration not necessarily related to changes in the plasma, and (*c*) changes in the cells of the proximal convolution. The diuresis is the product of increased filtration, secretion and osmotic resistance to water resorption (the last is perhaps a result of the presence of excess chloride in the lumen of the distal half of the tubule). With reference to mercury, this statement is not invalidated by obviously inconclusive reports of (*a*) evidence against an increased rate of filtration in salyrgan diuresis, (*b*) the action of mercury on the isolated kidney and (*c*) the results of its injection into the renal artery of an anesthetized dog. Increased volume and rate of flow of fluid through the lumen readily cause the resorptive capacity of the tubule to be exceeded. When substances are excreted in amounts which impede their own resorption and that of water, there is small need for further conjecture regarding the cause of the diuresis. Mercury does not affect appreciably the resorptive capacity of the tubule. Its action is limited chiefly to the proximal convolution, which has a minimal resorptive capacity. The glycretic diuresis which often results from the action of mercury is caused by the presence of abnormal amounts of dextrose and chloride in the lumen of that part of the tubule distal to the proximal convolution. I have some evidence, however, that mercury can so affect this convolution that water and solutes pass as readily through its cells as through those of the corpuscle. If so, a diuresis could occur owing to the increased volume of flow through the tubule, in excess of its resorptive capacity. That the known capacity of the distal half of the tubule to resorb water, chloride, bicarbonate and possibly urea is but little, if at all, affected by the action of mercury is shown by appropriate decrease in the volume or rate of flow through the tubule, by the work done in resorption during diuresis, and by the results from injections of the antidiuretic hormone.

DIURESES AND RENAL OXYGEN CONSUMPTION

Available data indicate that the kidney has a high metabolism, in some forms of diuresis it may consume as much as 10 per cent of the oxygen consumed by the whole body. This is not surprising in view of the work done by the cells of the tubule in secretion, synthesis and resorption. In secretion, work is needed for the transfer of solutes from solutions presumably of higher to those of lower osmotic pressure while, at the same time and site, dextrose and perhaps phosphate pass through the lumen in the opposite direction. It is improbable that any effective

filtration pressure obtains in the peritubular capillaries (except possibly for a short distance from the efferent arteriole) unless it is transmitted to them through arteriovenous anastomoses. Therefore, resorption, without work, could occur at least from the lumen of the middle third of the tubule (the thin segment and the lower part of the ascending limb). But soon the luminal fluid, because of the resorption of water, has a higher osmotic pressure than does the plasma, whose osmotic pressure decreases in consequence of this same resorption. Accordingly, work must be done to transfer the solutes in the lumen from a higher to a lower osmotic pressure.

It is noteworthy that when diuresis occurs after intravenous injections of urea, sodium sulfate or phlorhizin there is said to be a marked increase in renal oxygen consumption. Often, however, it does not occur when diuresis follows injections of Ringer's solution or of sodium chloride. Renal oxygen consumption increases in proportion to blood flow but not to urine flow.²⁴ Increase in the rate of urea excretion is attended by an increase in blood flow, but, according to one investigator,²⁴ there is no increase in oxygen consumption. The percentage of urea in the urine is also greatly reduced after injections of Ringer's solution while that of sodium chloride or of sodium sulfate is not. During the diuresis of excessive filtration, contingent on a reduction of plasma proteins, the renal oxygen consumption is not increased. In other words, there is no increase in work done by the tubule. But when the proximal convolution is impaired by phlorhizin the accompanying diuresis involves a significant increase in oxygen consumption, although dextrose is presumably not resorbed by parts of the tubule other than this convolution, which under the action of phlorhizin cannot resorb it. This seems paradoxical, since phlorhizin appears not to affect the excretion and relative resorption of other urinary constituents. But account should be taken of the possibility that periods of heightened secretory activity in one part of the tubule may not coincide with similar periods of resorptive activity in another part, also, oxygen consumption by the cells of the proximal convolution may be reduced while that by the cells of the remainder of the tubule is not. Therefore, an increase in oxygen consumption by one part of the tubule may approximate or be identical with a decrease in another part, without significant change in the total amount of oxygen consumed. Since the glomerulus functions at the expense of the pumping heart while oxygen for the tubule is locally obtained, diuretics may not reveal consistent changes in renal oxygen consumption because of the important part played by the highly variable glomerulus in most diureses and because the limits of tubular activity are relatively fixed.

24 Van Slyke, D. D., Rhoads, C. P., Miller, A., and Alving, A. S. Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption, and Diuresis. The Mechanism of Urea Excretion, *Am J Physiol* **109** 336-374 (Aug.) 1934.

CONCLUSION

1 In the kidneys of all classes of vertebrates the proximal convolution is primarily secretory and is the only part of the tubule invariably present. The structure and functions of the tubule, when viewed phylogenetically and when studied in health and in disease, would seem to have an importance much greater than is at present demonstrable in detail. Comparative renal studies dealing with the aglomerular kidney, and inaugurated by me in this connection, have been productive of much interest in secretion by the tubule. It is hoped that eventually the actual role of the tubule in urine formation will be established.

2 The phylogenic development of the corpuscle as the site of filtration is related to that of the distal convolution as the site of resorption. Filtrable substances in the plasma are excreted by the corpuscle regardless of possible depletion of body fluids and consequent damage to the tissues. The distal convolution, aided in birds and mammals by the thin segment and the ascending limb of the medullary loop, performs by resorption the function of salvage. The hypotonic urine of cold-blooded animals indicates that there has been resorption of relatively more of certain solutes than of water, the hypertonic urine of warm-blooded animals indicates the opposite.

3 A filtrable fraction of plasma is excreted into the lumen of the tubule by the corpuscle and by the cells of the proximal convolution. Minimal amounts of protein are present in this fraction because the passage of larger amounts is prevented by the epithelial wall adjacent to the glomerular and peritubular capillaries. Many factors so affect filtration by the corpuscle, however, that albuminuria readily develops. The extreme sensitiveness of this structure to such normal or pathologic changes as those which occur in the chemical composition of plasma or in blood pressure, flow or volume is responsible for confusing variations and dubious interpretations of its activity.

4 Diuretics are initially and chiefly effective by their direct or indirect action on one or more of the components of the cardiovascular system. Neither diuretic urine nor the subnormally concentrated urines formed after renal injury should be regarded as necessarily indicating impairment of the resorptive power of the tubule. Urines of low specific gravity may be variously formed as a result of excessive filtration, of decreased resorption of water or of increased resorption of solutes.

5 It is not yet established that the formation of urine is primarily the result of filtration and resorption or that resorption is the chief function of the tubule as a whole.

EFFECT OF SULFANILAMIDE AND SULFAPYRIDINE ON HEMOGLOBIN METABOLISM AND HEPATIC FUNCTION

C J WATSON, M D

AND

W W SPINK, M D

WITH THE TECHNICAL ASSISTANCE OF RUTH L EVARTS
MINNEAPOLIS

Since sulfanilamide has come into general use, a number of reports have appeared indicating that jaundice¹ and hemolytic anemia² are toxic effects that may be encountered. One gains the impression from the majority of these reports that such complications are rarely encountered and that they are probably due to drug idiosyncrasy. Long and his associates^{1a} observed but 2 patients with jaundice (without hemolytic anemia) among 408 treated with sulfanilamide. In the material from the same clinic, Wood^{2b} noted that acute anemia developed in 21 of 522 persons to whom the drug was administered. He found the incidence of anemia to be 8.3 per cent in children as compared with 2.4

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1 (a) Hageman, P. O., and Blake, F. G. A Specific Febrile Reaction to Sulfanilamide. Drug Fever, *J. A. M. A.* **109** 642 (Aug. 28) 1937. (b) Saphirstein, H. Hepatitis and Toxic Erythema with Desquamation Due to Sulfanilamide, *Urol. & Cutan. Rev.* **42** 101, 1937. (c) Bannick, E. G., Brown, A. E., and Foster, F. P. Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds, *J. A. M. A.* **111** 770 (Aug. 27) 1938. (d) Lockwood, J. S., Coburn, A. F., and Stokinger, H. E. Mechanism of Action of Sulfanilamide, *ibid.* **111** 2259 (Dec. 17) 1938. (e) Garvin, C. F. Toxic Hepatitis Due to Sulfanilamide, *ibid.* **111** 2283 (Dec. 17) 1938. (f) Cline, E. W. Acute Yellow Atrophy of the Liver Following Sulfanilamide Medication, *ibid.* **111** 2384 (Dec. 24) 1938. (g) Long, P. H., Bliss, E. A., and Feinstein, W. H. Mode of Action, Clinical Use and Toxic Manifestations of Sulfanilamide, *ibid.* **112** 115 (Jan. 14) 1939. (h) Watson, C. J. The Effect of Sulfanilamide upon the Liver, *Surgery* **5** 616, 1939.

2 (a) Harvey, A. M., and Janeway, C. A. The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide, *J. A. M. A.* **109** 12 (July 3) 1937. (b) Wood, B. Anemia During Sulfanilamide Therapy, *ibid.* **111** 1916 (Nov. 19) 1938. (c) Erf, L. A., and MacLeod, C. M. Hemolysis from Sulfapyridine, *J. Clin. Investigation* **18** 472, 1939.

per cent in adults. He ascribed the anemia in the 21 cases to hemolysis, because of the abrupt appearance of jaundice and urobilinuria. In 8 additional instances a "slow" type of anemia was encountered, which was similar to that previously described by Jennings and Southwell-Sander.³ Wood was unable to determine whether this type was due to sulfanilamide or to the underlying disease. Erf and MacLeod^{2c} have recently reported a regular increase in the rate of hemolysis in patients with pneumonia receiving sulfapyridine.

The present study was made with the purpose of determining the effects of varying doses of sulfanilamide and sulfapyridine on hepatic function and hemoglobin metabolism. We were primarily interested in determining whether the administration of either drug regularly produced evidence of hepatic dysfunction and increased destruction of blood. It was hoped that information would be obtained with respect to whether the occasional occurrence of jaundice and hemolytic anemia represents an accentuation of usual toxic effects or a true drug idiosyncrasy.

MATERIAL AND METHODS

During the past two years we have recorded the therapeutic activity of sulfanilamide in 110 and of sulfapyridine in 44 cases of various types of infection. Sixteen cases of distinct or marked jaundice were observed, all the patients were in the group receiving sulfanilamide. Although this will convey some idea of the frequency of jaundice after sulfanilamide therapy, the figures just given cannot be looked on as representing a true incidence. The great majority of the 110 patients treated were in the medical service of the University Hospital. Several of the patients with jaundice, however, were in the surgical service or other services, and while we have seen all of the jaundiced patients, we recognize that an indeterminate number of patients not included in our records have been treated with sulfanilamide. While the number of sulfapyridine-treated patients is an exact total, therapy had to be abandoned early in a considerable percentage of instances because of nausea and vomiting. Therefore, although we have encountered no instances of jaundice following administration of sulfapyridine, it is realized that the number of patients given the substance in the doses usually effective is too small to permit definite conclusions.

The data to be presented were obtained from two groups of cases. 1. The first was composed of 8 patients who were selected for study prior to the administration of sulfanilamide or sulfapyridine. The nature of the infection in these cases was such that therapy could be postponed for a number of days, during which control observations were made. Various determinations were made before, during and after administration of the drug. They included determination of the value for plasma bilirubin, of the urobilinogen content of a twenty-four hour sample of urine, of the per diem amount of urobilinogen in the feces for consecutive four day periods, of the levels of free and total sulfanilamide or sulfapyridine in the blood, of the hemoglobin content, of the number of erythrocytes, and of the percentage of reticulocytes. The value for urinary coproporphyrin was determined in 4 of the 8 cases. 2. The second group of patients numbered 28. The data

3 Jennings, G. H., and Southwell-Sander, G. Anemia and Agranulocytosis During Sulfanilamide Therapy, *Lancet* 2: 898, 1937.

obtained from this group are less complete and vary in extent in different instances. The study in these cases was not planned as it was for the patients in group 1, consequently the various observations which will be noted were usually made only after administration of the drug had been commenced and often only after the development of definite jaundice or anemia. This group is composed chiefly of cases in which jaundice appeared after administration of sulfanilamide, in 3 of the cases, as will be noted subsequently, the drug was placed in the peritoneal cavity at the time of operation in the hope of preventing peritonitis following perforation in the gastrointestinal tract. Observations are included in which there was evidence of reduced hepatic function without jaundice, also, cases are included in which smaller doses of the drug were without untoward effect on the liver or on the blood.

Two additional cases of icterus were omitted because of the likelihood that pulmonary infarction was present. Both of the patients suffered from patent ductus arteriosus and vegetative endocarditis.

The following methods were employed. The blood sulfanilamide and sulfapyridine levels were determined by the method of Marshall and Litchfield.⁴ The urobilinogen content of the urine and feces was determined by the Terwen⁵ method as modified by Watson.⁶ The normal range of values with this method are 0 to 3 mg per day for the urine and 40 to 280 mg per day for the feces. The urinary coproporphyrin was estimated in twenty-four hour samples of urine by means of the procedure described by Fikentscher,⁷ slightly modified.⁸ This method depends on ether extraction of the acid urine, removal of the coproporphyrin with dilute hydrochloric acid and quantitative determination by measurement of the intensity of red fluorescence excited by ultraviolet rays. The measurement is made with a Zeiss *Stufenphotometer* and a standard coproporphyrin solution. It is believed that the normal range with this method is 30 to 100 γ per day. The value for plasma bilirubin was determined by the Jendrassik and Czike⁹ modification of the van den Bergh method.¹⁰ The Zeiss

4 Marshall, E. K., Jr., and Litchfield, J. T., Jr. The Determination of Sulfanilamide, *Science* **88** 85, 1938.

5 Terwen, A. J. L. Ueber ein neues Verfahren zur quantitative Urobilin Bestimmung in Harn und Stuhl, und über die Bereitung und die Eigenschaften von einem möglichst reinem Urobilinpräparat, *Deutsches Arch f klin Med* **149** 72, 1925.

6 Watson, C. J.: (a) Studies of Urobilinogen. I. An Improved Method for the Quantitative Estimation of Urobilinogen in Feces and Urine, *Am J Clin Path* **6** 458, 1936, (b) II The Per Diem Excretion of Urobilinogen in Urine and Feces by Normal Individuals, and by Patients Having Diseases Not Primarily Affecting the Liver or Biliary Tract, *Arch Int Med* **59** 196 (Feb.) 1937, (c) III The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Liver Disease, *ibid* **59** 206 (Feb.) 1937.

7 Fikentscher, R. Quantitative Porphyrin—Bestimmung durch Lumineszenz intensitätsmessung mit dem Stufenphotometer, *Biochem Ztschr* **149** 257, 1932.

8 Details of this modification will be described elsewhere.

9 Jendrassik, A. C., and Czike, A. Bestimmung des Bilirubins im Blute, *Ztschr f d ges exper Med* **60** 554, 1928.

10 In accordance with an observation made by Dr. I. J. Pass, working in this laboratory, that maximum coupling is effected only if larger amounts of sodium nitrite are used in diazotizing the sulfanilic acid, we have employed 0.4 cc of 0.5 per cent sodium nitrite for each 9.6 cc of 0.5 per cent sulfanilic acid, rather than 0.1 cc as recommended by Jendrassik and Czike.⁹

Stufenphotometer was employed as recommended by Heilmeyer and Krebs¹¹ Because of the considerable variation in hepatic function,¹² the upper limit of normal is somewhat arbitrary, for the great majority of normal persons the range is from 0.30 to 1.0 mg per hundred cubic centimeters The value for hemoglobin was determined in terms of grams per hundred cubic centimeters by means of the Sheard-Sanford photometer¹³ Reticulocytes were counted in dry smears prepared in the following manner Thin, uniform smears of a 1 per cent alcoholic solution of brilliant cresyl blue were made on ordinary glass slides As soon as these were dry, very thin blood smears were superimposed on the dye in the usual way, the wet smears were at once placed in a moist chamber (a Petri dish or a staining jar containing wet filter paper on the bottom) After ten minutes the smears were removed and rapidly dried by whipping They were not counterstained, since we have noted a regular lowering of the reticulocyte percentage when this is done With this method the normal range is from 0.5 to 1.5 per cent Data relating to the size and hemoglobin content of the erythrocytes were obtained by means of the Wintrobe hematocrit tube¹⁴ and the Pijper halometer (Zeiss)

RESULTS

The data for the 8 cases in group 1 have been recorded graphically and are shown in charts 1 to 6 inclusive The clinical data and laboratory findings in the cases of group 2 are given in table 1 Additional data relating to the erythrocytes are given in table 2

COMMENT

Hemoglobin Metabolism—This may be defined as the relation between the rates of blood destruction and blood regeneration as measured by the output of urobilinogen in the feces and the reticulocyte percentage¹² Evidence of increased hemoglobin metabolism was noted in all cases in which data were obtained relative to the rate of blood destruction and regeneration A varying degree of increase of urobilinogen in the feces and of the reticulocyte percentage is noted in the data for cases 1 to 8, inclusive (charts 1 to 6) A marked increase of urobilinogen in the feces was likewise noted in cases 20 and 25 (table 1), in both of which the hemoglobin and erythrocyte levels rapidly declined Increases in serum bilirubin and urine urobilinogen which occurred are regarded as chiefly due to hepatic dysfunction and will be considered

11 Heilmeyer, L., and Krebs, W. Spektrophotometrische Untersuchungen des Ehrlich-Proscherschen Bilirubin—Azofarbstoffes und ihre praktische Anwendung, besonders zur quantitativen Bestimmung des Bilirubins im Blutserum, *Biochem Ztschr* **223** 352, 1930

12 Watson, C. J. The Pyrrol Pigments with Particular Reference to Normal and Pathologic Hemoglobin Metabolism, in Downey, H. Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2445

13 Manufactured by the Central Scientific Co.

14 Wintrobe, M. M. The Size and Hemoglobin Content of the Erythrocyte Methods of Determination and Clinical Application, *J. Lab. & Clin. Med.* **17** 899, 1932

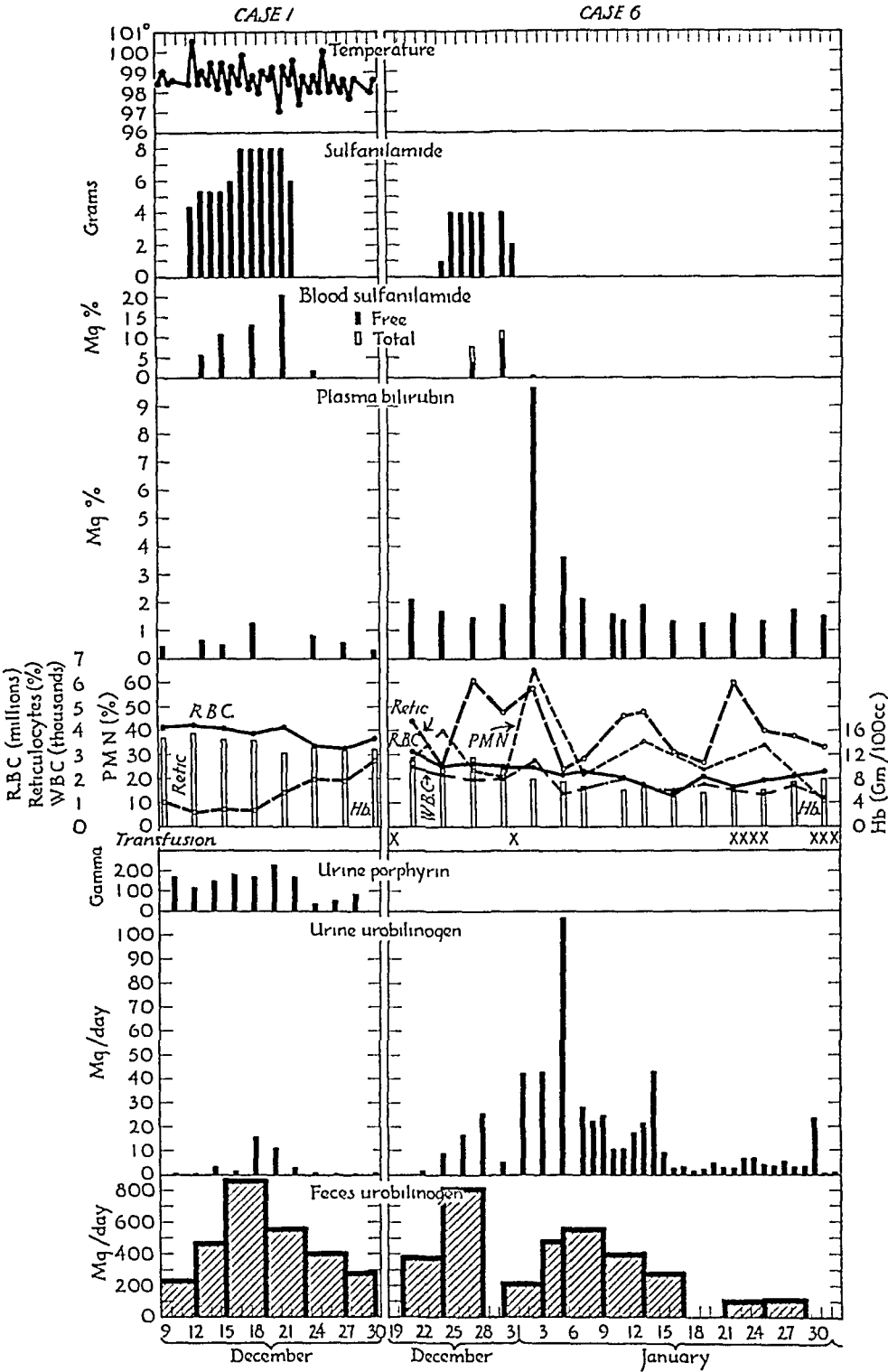


Chart 1—Records of L G, a man aged 54 (case 1), and K B, a woman aged 48 (case 6). In the case of L G there was chronic brucellosis of eight months' duration. Marked improvement followed sulfanilamide therapy. In the case of K B there was probable subleukemic splenic reticuloendotheliosis. Sulfanilamide therapy was given for gluteal abscess following injection of liver extract.

in this relation later. Exact correlation of the time of appearance and duration of increased hemolysis with the dosage and with the blood level of sulfanilamide was not possible because of varying lag in excretion of urobilinogen in the feces. This is a variable which is incident to the rate at which the feces traverse the intestinal tract. It is best

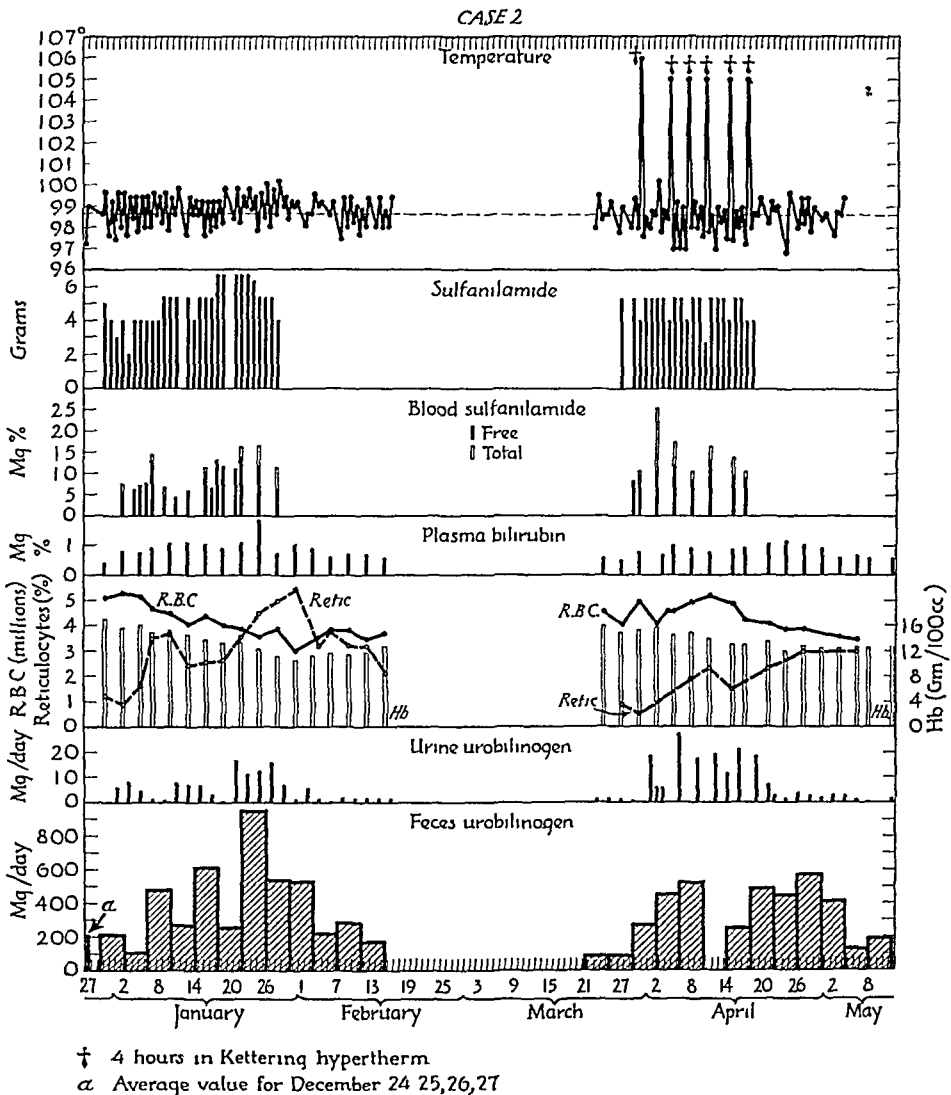


Chart 2 (case 2)—Record of J. F., a man aged 37. There was chronic brucellosis (duration three years). No improvement followed sulfanilamide therapy or sulfanilamide plus fever therapy.

illustrated in case 8 (chart 5), in which constipation interfered with regular collection of feces. In this instance the amounts of urobilinogen noted for the four day periods ending on March 30 and April 3 were very small, probably because of the very small amounts of feces obtained by means of repeated enemas. In the next period (April 4 to 6), however, the bowel movements were spontaneous and regular, and a very

large amount of urobilinogen was noted in the feces. There can be no doubt that part of this, at least, represented destruction of blood which had occurred during the earlier periods. For this reason an average value for the three periods is recorded.

In general, it is evident from the data on the 8 cases in group 1 (charts 1 to 6) that increased hemolysis of some degree appeared within

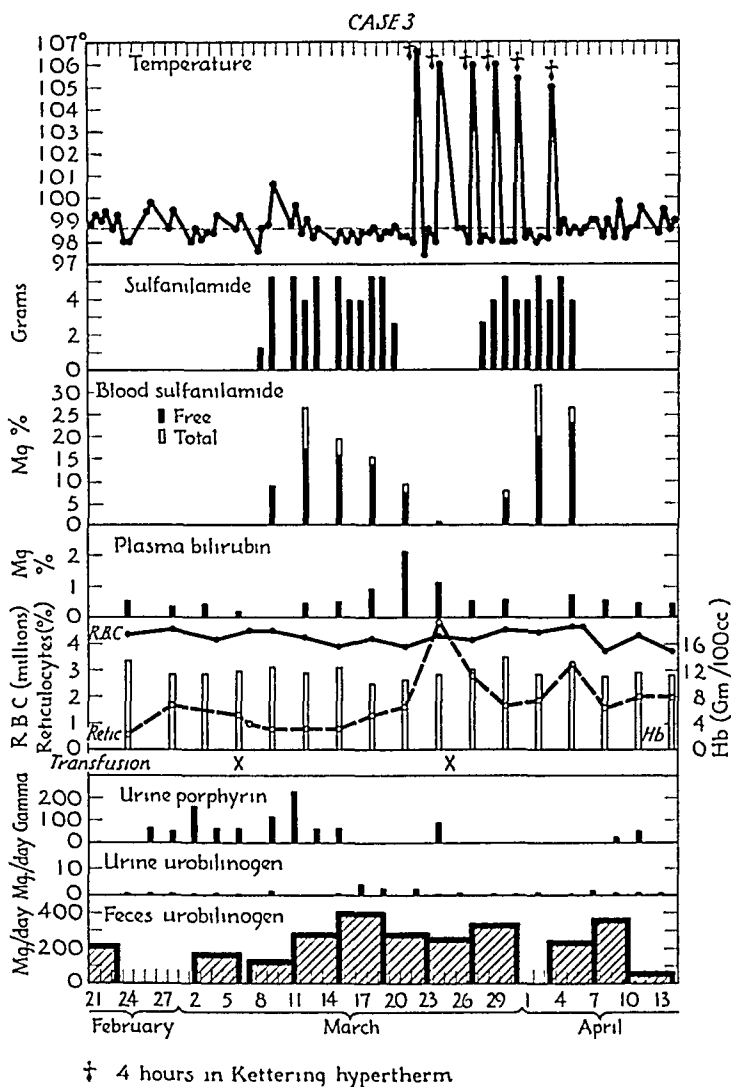


Chart 3 (case 3)—Record of W. R., a man aged 31. There was chronic gonorrheal arthritis. Improvement followed sulfanilamide plus fever therapy.

four to eight days after administration of sulfanilamide or sulfapyridine, that it was usually most marked with higher blood levels of the drug or soon after the occurrence of such levels and that it subsided within a few days after administration had been discontinued. One exception has been noted in respect to time of subsidence, this was in case 2 (chart 2). It is of considerable interest that in this case the urobilinogen content of the feces became markedly elevated during sulfanilamide

therapy, returning to normal within six days after administration of the drug was stopped. In a later period, a combination of sulfanilamide and fever therapy resulted in a second elevation of urobilinogen in the feces, and the increased hemolysis persisted this time for sixteen days. The cause of this persistence was not determined. The data in general do not suggest that fever produces any increase in the hemolytic action of the drugs. Treatment with artificially induced fever combined with

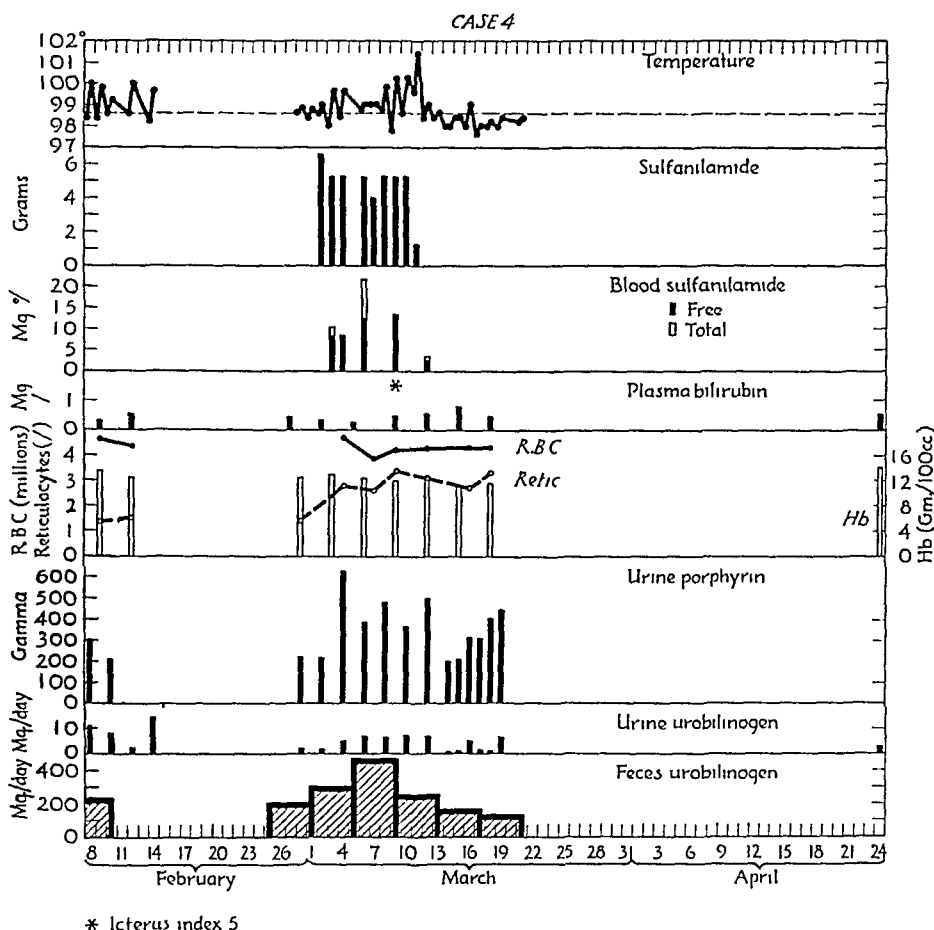


Chart 4 (case 4)—Record of C D, a man aged 39. There was chronic rheumatoid arthritis. No improvement followed sulfanilamide therapy.

sulfanilamide in another instance (case 3 [chart 3]) was not associated with any greater increase of hemolysis than was noted as following administration of sulfanilamide alone.

A comparison of the effect on blood destruction of relatively large and small amounts of the drug during different periods has been carried out in but 1 instance (case 7). The patient received sulfapyridine. In chart 6 it may be noted that the value for urobilinogen in the feces reached 744 mg per day within six days after a blood sulfapyridine level of 10.2 mg per hundred cubic centimeters had been attained. The use

of the drug was discontinued for five days and then resumed with smaller doses (1.5 Gm daily for four days). At the end of this period the blood level was 6.2 mg per hundred cubic centimeters. This was associated with a mild increase of hemolysis lasting at least through

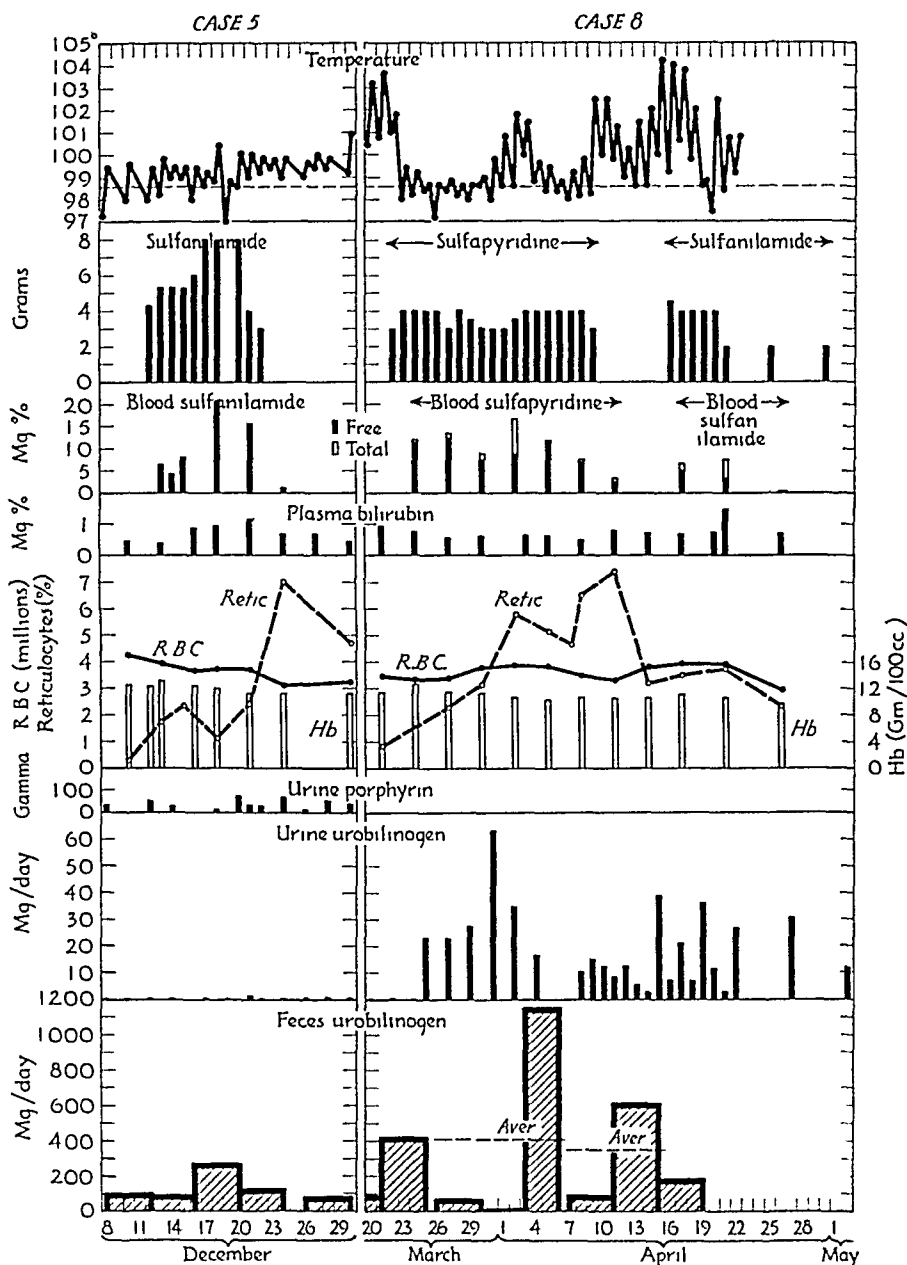


Chart 5—Records of E. S., a girl aged 17 (case 5), and B. B., a man aged 32 (case 8). In the case of E. S. there was low grade chronic rheumatic fever. The patient was unimproved after sulfanilamide therapy. In the case of B. B. there was subacute bacterial (*Streptococcus viridans*) endocarditis. The patient was unimproved after sulfanilamide and sulfapyridine therapy. The significance of the averages indicated by the broken line is discussed in the text.

Jan 11, 1939. From January 19 until February 6, 0.5 Gm was given daily. During this period the fecal urobilinogen remained at low normal levels, and there was no further evidence of increased hemolysis.

The fact that administration of sulfapyridine is followed by increased blood destruction (cases 7 and 8) is believed to be of significance with respect to the question of the possible relation of methemoglobinemia to increased output of urobilinogen in the feces. In neither case 7 nor case 8 was cyanosis observed. Although examination of the blood for methemoglobin was omitted, we believe that the absence of cyanosis excludes the presence of any appreciable degree of methemoglobinemia.¹⁵ We have rarely observed methemoglobinemia in our patients receiving

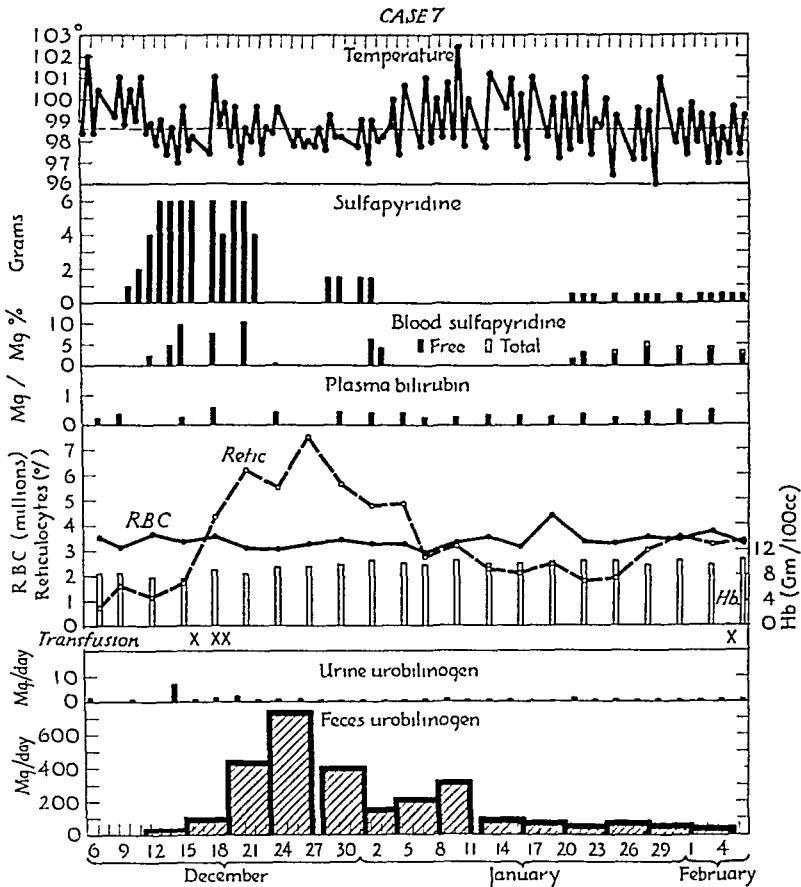


Chart 6 (case 7) —Record of R. K., a woman aged 25. Subacute bacterial (viridans) endocarditis was present. Temporary improvement followed sulfanilamide therapy.

sulfapyridine. Thus, it is highly unlikely that methemoglobinemia bears any relation to increased hemolysis. This, of course, is also borne out by the frequent observation of marked cyanosis following administration of sulfanilamide without development of any appreciable degree of anemia.

¹⁵ Watson, C. J., Vigness, I., and Spink, W. W. Relation of Methemoglobin to the Cyanosis Observed After Sulfanilamide Administration, *Proc Soc Exper Biol & Med* 40: 547, 1939.

The values noted in case 6 (chart 1) require particular mention. It is seen that mild hemolytic anemia of macrocytic type was present prior to sulfanilamide therapy. This was of the type not infrequently associated with leukemia and reticuloendotheliosis¹⁶. Shortly after sulfanilamide therapy was commenced the urobilinogen content of the feces increased, and the anemia became much more marked. The use of the drug was discontinued, after which there was rapid decrease in jaundice, although the anemia gradually increased in association with a persistent elevation of the value for urobilinogen in the feces. This persistence of increased hemolysis is regarded as part of the underlying disease, it may be pointed out that the values recorded for January 25 and 29 are still elevated when the total amount of circulating hemoglobin is considered¹². By that time, however, the rate of blood destruction had decreased sufficiently so that the increased reticulocyte percentage resulted in a distinct increase of hemoglobin and erythrocytes.

It is noteworthy that the patient in case 6 exhibited marked neutropenia prior to use of sulfanilamide but that prolonged administration of the drug was not productive of any appreciable further decrease of the neutrophils.

The data in cases 1 to 8 indicate that the degree of anemia is dependent primarily on the degree of increased hemolysis and secondarily on the reticulocyte response. The major drop in hemoglobin and red blood cells is seen to be related closely to the periods in which the largest amounts of urobilinogen were found in the feces. In general, there is evident correlation between the degree and duration of the anemia and the extent of the reticulocyte response. In case 7 (chart 6), in which the reticulocyte response was relatively marked, no decline in the hemoglobin level occurred. In case 5 (chart 5) an unexplained discrepancy was noted between the values for reticulocytes, hemoglobin and feces urobilinogen. The last-mentioned value was slightly increased during the period from December 16 to 20. A slight decline in the level of hemoglobin followed, and the percentage of reticulocytes then rose to 7. In spite of this evidence of active regeneration, the hemoglobin level did not increase, although the urobilinogen determinations failed to reveal evidence of blood destruction. It is possible, of course, that more than the usual absorption of urobilinogen in the intestine was taking place in this instance, and if this were true the rate of blood destruction would have been more rapid than was apparent.

Although it is clear from the foregoing facts that some degree of increased blood destruction may follow administration of sulfanilamide

16 Watson, C. J. Hemolytic Jaundice and Macrocytic Hemolytic Anemia. Certain Observations in a Series of Thirty-Five Cases, *Ann Int Med* **12** 1782, 1939.

TABLE 1—Clinical and Laboratory Data in Group 2

Case No. Patient Sex, Age	Diagnosis and Complications	Amount of Sulfanilamide, Periods Given, and Blood Level				Urine Urobilin nogen, Mg per Day	Hemo- globin, % (Sahl)	Date	Red Blood Cells, Millions per Cubic Mm	Date	Comment
		Amount per Day	Level of Free Sulf- anil- amide	Icterus Index or Serum Bilirubin	Date						
9 J M F 23	Bronchopneumonia and hemolytic streptococ- cus empyema	12/13 to 12/14 7 Gm	17.5	I I 14 8	12/13 12/15 12/19	25.7 1.3	81 61	12/17 12/19		12/11 12/17	Icterus noted on 12/15, had disappeared by 12/19, recovery after several weeks of fever
10 M F 29	Hodgkin's disease, in tercurrent pyelo- nephritis	7/5 0.33 Gm 7/6 to 7/16 1.33 Gm 7/16 0.33 Gm	2.3 2.6		7/11 7/11	6.2 1.5 0.7 4.6 2.8 1.6 3.2 4.1 3.9	66 65	7/4 7/5 7/6 7/7 7/9 7/11 7/13 7/15 7/17		7/7 7/16	Hodgkin's disease relatively quiescent (laminectomy for cord involvement in 1936), no icterus during sulfanilamide therapy
11 L M 50	Carcinoma of stom- ach, perforation, peri- tonitis, laparotomy and closure of per- foration	10 Gm of crystals placed in peritoneal cavity at oper- ation, 2.15 p m, 2/4/39	7.2 15.1 6.6 Trace	88 103 122	2/9 2/13 2/15	10.9	63 59 72	2/14 2/9 2/13		2/3 2/9 2/13	No icterus prior to operation, first noted 2/6, rapidly became intense, seven blood trans- fusions (400-1,000 cc) 2/4 to 2/13, died 2/16
12 H L M 44	Bowel obstruction, laparotomy, acciden- tal perforation	12 Gm of crystals placed in peritoneal cavity at oper- ation on 12/24, 2 Gm subcutan- eously on 12/25 and 12/26	20.8 15.0 6.3 3.5	213 361 240 203	12/26 12/28 12/29 12/30	11.1	88 76	12/30 12/30 12/30 12/30		12/26 12/30	No icterus prior to operation, first noted 12/25, rapidly became intense, 800 cc blood trans- fusion on 12/24, 1,600 cc on 12/25, 600 cc 12/30, died 12/31
13 L R F 29	Subacute bacterial (viridans) endocar- ditis, old rheumatic mitral valve defect	7/17 to 8/19 1 Gm	7.8 9.0 10.6 13.2 13.0 11.0 4.0 6.0	6 2.2 S B	7/21 7/25 7/28 8/1 8/4 8/8 8/15 8/16	0.7 1.0 6.5 2.6 0.6 1.4 0.7 21.8 49.0 32.5 26.9 21.0	45 35 47 52 56 63 68 8/5 8/8 8/10 8/12 8/14	7/16 7/20 7/22 7/25 7/25 7/30 7/31 8/5 8/8 8/10 8/12 8/14		7/13 7/20 7/22 7/25 8/3 8/5 8/23	Seventeen blood transfusions, 100 to 400 cc

14 A M F 31	Probable bacillary dysentery, cecal ab- scess, B coli septi- cemia	12/20 to 12/21 5 Gm 12/31 5 Gm	9 0	12/22	II 7 9 7 32 28 22	12/14 12/22 12/28 1/4 1/12 1/13	3 7	12/22	81 79 64 45 35 80	12/5 12/7 12/21 12/27 1/4 1/13	2 7	12/27	Continuous irregular fever, no diarrhea during period of ob- servation, many blood trans- fusions between 12/20 and 1/12, died 1/14
15 L S F F 22	Acute benign lymphad- enosis (infectious mononucleosis)	6/22 to 6/24 13 Gm 6/25 4 Gm 6/26 3 Gm	7 1	6/24	17 0	6/24	19 5 21 6 17 15 10	6/26 6/28 6/30 7/1 7/5					Jaundice noted 6/27, fever per- sisted through 7/1, much less after 7/1, urticarial rash 6/28, no improvement noted after sulfanilamide
16 I P I 11	Carcinoma of cervix, peritonitis following high voltage roent- gen therapy	11/11 3 Gm 11/15 to 11/18 1 Gm			16 45 13	11/9 11/18 11/22	PD PD PD		52 36 39 54 63 84	10/28 11/7 11/9 11/15 11/30 1/11	3 96 3 12 3 5 3 6	10/28 11/7 11/9 11/30	Slight icterus noted prior to therapy, marked increase after sulfanilamide, rapid disappearance when discon- tinued, roentgen therapy com- menced on 11/7, repeated blood transfusions 11/6 to 11/17
17 G A M 64	Prostatic obstruction, pyelonephritis, trans- urethral resection	1/6 to 1/17 1 Gm	12 1 7 2 1 2	1/8 1/10 1/11	23 12 10	1/14 1/16 1/21	++	1/17	74 68 73	1/1 1/17 2/2			Jaundice first noted on 1/14, discharged on 3/3/38, much improved
18 G P M 10	Recurrent gonorrheal arthritis	8/3 to 8/16 1 Gm	2 1 5 7 7 8	8/8 8/9 8/15	S B 0 73 0 61	8/2 8/13	18 8 6 3 5 15 3 7 3 19 4 10 2	8/1 8/3 8/5 8/7 8/9 8/11 8/13	87 75 78 75 75	7/29 8/7 8/10 8/13 8/16			No jaundice, discharged mark- edly improved on 8/19/38
19 M O F 54	Hemolytic streptococ- cus septicemia (from infected wound), secondary cellulitis, jaundice with enlarged liver	2/18 to 2/22 1 Gm 3/11 to 3/14 1 Gm 9 Gm (total) between 3/17 and 3/19, inclusive			II 32 63	3/15 3/17	5 6	3/17	81 79 76 71	3/14 3/16 3/17 3/18			Continuous marked septic fever, no improvement after sulfanilamide, progressively deepening jaundice died 3/19/39
20 F S M 11	Chronic osteomyelitis, acute exacerbation, sequestrectomy	5/23 to 5/27 5 3 Gm			10	5/30	307 0 73 5 38 6 25 1 7 5 10 7 5 1 1 6	5/31 6/1 6/2 6/3 6/4 6/5 6/6 6/15	61 32 31 61 84 85	5/17 5/27 5/29 5/31 6/8 6/13			Negative blood cultures, jaun- dice noted on 5/26 had dis- appeared by 5/30 reticulocytes 2.2% on 5/29, feces urobilinogen markedly elevated 813.8 mg per day, 5/27 to 5/31, marked improvement after discontinu- ance of drug continuous marked fever until 5/30

TABLE 1—Clinical and Laboratory Data in Group 2—Continued

Case No., Patient Sex, Age	Diagnosis and Complications	Amount of Sulfanilamide, Periods Given, and Blood Level										Icterus Index or Serum Bilirubin	Urine Urobilinogen, Mg per Day	Hemo globin, % (Sahl)	Date	Red Blood Cells, Millions per Cubic Mm	Comment
		Amount per Day	Level of Free Sulfanilamide		Date	Serum Bilirubin	Van den Bergh Test	Date (Sahl)	Date	Date							
			Sulfanilamide	Free Sulfanilamide													
21 N M	Pneumonia, empyema	12/11 to 12/19 4 Gm	4.3	2.7	12/13	20	12/19	PD			86	12/6				Sulfanilamide discontinued on 12/19 because of appearance of jaundice, no improvement, continuous septic fever, died	
21 M			6.9	7.0	12/16	24	12/21	PD			78	12/21					
21 M					12/17	10	12/23										
22 G M	Epididymitis, hemo-lytic streptococcus recovered from blood, hypertension, cerebral and coronary arteriosclerosis	3/17 to 3/22 4 Gm	6.0	7.0	3/22	29	3/23	Biphasic			66	3/16	2.7	3.16		Sulfanilamide discontinued because of icterus epididymitis and bacteremia disappeared, fever diminished in spite of increasing stupor, decubitus ulcers	
78 M			6.2		3/23	21	3/24	PD			65	3/16	2.3	3.16			
					3/24	7	3/31				55	3/30	2.0	3.30			
					3/24	8	4/6				50	4/4					
23 G W	Squamous cell carcinoma (cervix) with pulmonary and pleural metastases, empyema, hemoptysis	3/3 to 3/8 6 Gm	9.0	14.0	3/4	5	2/27			39.7	3/8	51	3/2	3.91	3/6	Jaundice noted on 3/6, patient irrational and very toxic on 3/7, spiking fever, blood transfusions on 3/13 and 3/14, rib resection, biopsy 3/10	
44 T		3/9 to 3/10 3 Gm			3/6	27	3/6	PD			55	3/6	2.0	3/13			
						3.4	3/7				32	3/13					
											48	3/15					
24 R H M 61	Pyonephrosis, nephrectomy	4/15 3.6 Gm 4/16 4.16 3.3 Gm 4/18 to 4/23 1.3 Gm			4/24	4.76	4/24	PD	61.8	4/24	52	4/24	2.8	4/24	4/24	Marked improvement	
					4/27	1.27	4/27	PD	39.3	4/25	49	4/27	2.5	4/27	5/1		
					4/30	1.06	4/30	PD	25.4	4/27	54	5/1	3.4	5/1			
									32.5	4/29							
25 R N M	Toxic hepatitis following pneumonia, sulfanilamide given by local physician because of recurrence of fever on 4/15, three days after effective use of anti-pneumococcal serum for type III pneumonia	4/15 to 4/18 6.6 Gm (total)	Trace		4/23	I I	4/22	PD	87.3	4/25	68	4/24	3.68	1/24		Slight icterus said to have been present before sulfanilamide marked jaundice first noted on 4/19 feces urobilinogen in mg per day	
						50	4/24	PD	221.1	4/27	59	4/27	3.28	4/27			
						8.4	4/25	PD	11.7	4/30	49	4/30	3.06	5/3			
						I I	4/27		86.1	5/2	46	5/3	2.7	5/6			
						3.3	4/27				45	5/6	3.2	5/9			
						I I	4/27				45	5/6		5/11			
						20	4/30	PD			45	5/9	4.6	5/15			
						S B	5/1				51	5/12					
26 E P F	Pyelonephritis	3/12 1.3 Gm 3/13 3 Gm 2.0 Gm	7.7	8.6	3/16 8 a m 3/16 10 a m 3/24 3/27	S B	3/2		1.4	3/2	76	2/28	4.4	2/28		No icterus, collections of feces for urobilinogen determination were prevented because of marked constipation and lack of cooperation	
						0.9	3/9		0.5	3/9	65	3/9	4.3	3/9			
						0.57	3/12		tr	3/11	68	3/12	4.1	3/12			
						0.74	3/15		0.3	3/13	66	3/15	3.7	3/15			
						0.72	3/18		tr	3/15	62	3/18	3.7	3/18			

27 E K M	Postpneumonic empy- ema (streptococci)	1/20 5.6 Gm 1/21 to 1/22 5.0 Gm 1/23 to 1/27 6.0 Gm 1/28 5.0 Gm 1/30 to 2/15 6.0 Gm	5.7 8.5 6.7 13.5 7.0 8.4 3.8 5.5 7.9	1/21 1/24 1/27 1/30 2/2 2/6 2/9 2/12 2/15	0.41 0.48 0.67 1.22 0.88 1.35 1.01 0.79 0.77 0.83 0.57 0.27	1/19 1/21 1/24 1/27 1/30 2/2 2/6 2/9 2/12 2/15 2/18 2/21	52.6 39.6 20.1 42.9 18.4 8.0 23.8 35.1 72.1 3.5	1/19 1/20 1/21 1/22 1/24 1/25 1/26 1/27 1/28	63 57 58 58	1/28 1/30 2/3 2/7	No icterus, recovery after rib resection and drainage on 2/15/39	
28 E K M	Post traumatic (auto mobile accident) peri- toneal abscess, stormy postoperative course, constant irregular fever, diminishing gradually after 2/7	12 Gm placed in peritoneal cavity at oper- ation 1/25 4 Gm IV 1/26 4 Gm IV 1/27 4 Gm IV 1/28 4 Gm IV 1/29 8 Gm IV 1/30 8 Gm IV 1/31 8 Gm IV 2/1 8 Gm IV 2/2 8 Gm IV	2.5 (15 min)† 2.9 5.3 5.4 5.9 7.0 6.8 6.7 5.8 3.0 4.9 7.6 6.6 7.0	1/25 30 min † 1 hr † 2 hr † 3 hr † 5 hr † 7 hr † 10 hr † 1/26 1/27 1/28 1/30 1/31 2/3								Left hospital much improved on 2/15, repeated blood trans- fusions 2/2 to 2/6, no icterus at any time

II = icterus index, S B = serum bilirubin in mg per 100 cc., PD = prompt direct, IV = intravenously

† Postoperatively

or sulfapyridine given in adequate therapeutic doses, our data on the size and hemoglobin content of the erythrocytes indicate that the anemia which may result differs from both the familial, or spherocytic, and the secondary, or macrocytic, hemolytic anemias¹⁶ The most significant difference is in hemoglobin content Instead of exhibiting a color index of 1 or above, tests revealed a value generally below 1 The color index was elevated in but 1 instance The patient (case 22) had mild macrocytic anemia before sulfanilamide therapy was commenced In case 2 the color index was 1.0, but this declined to 0.89 during the second period of therapy, when the hemoglobin level had again fallen In case 6 it is perhaps noteworthy that the color index fell from 1.06 to 0.95

TABLE 2—*Data on Size and Hemoglobin Content of Erythrocytes in Various Instances*

Case No	Date	MCV	MCH	MCC	MCD	Color Index	Hematocrit, Per Cent
2	2/15	116.7	34.8	30.0	8.4	1.0	42.9
	4/5	100.7	31.2	31.1	8.2	0.92	46.0
	4/27	112.4	32.8	29.2	8.4	0.96	43.8
3	2/24	88.4	30.8	34.9		0.91	38.7
	3/12	99.3	27.2	27.4	8.1	0.8	42.3
	3/15	106.4	32.2	30.3	8.1	0.94	41.6
	3/18	97.9	23.8	24.3	8.1	0.71	41.1
	3/21	97.2	27.0	27.7	8.3	0.8	38.2
	3/24	93.3	26.9	28.8	8.1	0.8	40.3
4	2/28	101.6	23.6	28.2		0.84	44.7
	3/12	102.1	28.0	27.5	8.2	0.83	43.7
	3/18	95.6	27.3	26.1	8.3	0.81	41.4
8	3/21	111.5	33.0	29.6	7.8	0.95	38.8
	4/11	111.1	31.8	28.6	8.2	0.92	37.0
	4/26	116.3	33.4	23.7	8.2	0.95	34.3

MCV = Mean corpuscular volume

MCH = Mean corpuscular hemoglobin

MCC = Mean corpuscular hemoglobin concentration

MCD = Mean corpuscular diameter

after sulfanilamide therapy, in spite of a marked increase in the rate of blood destruction with increasing jaundice and anemia While these variations are not regarded as significant in themselves, it is at least evident that the color index did not rise as might have been expected with hemolytic anemias of other causation Exact data as to size of the erythrocytes were available in cases 2, 3, 4 and 8 This is seen in table 2 The values given in table 2 may be compared with the data for cases 2, 3, 4 and 8, respectively, for the sake of correlation with the results of the other determinations which were made Although the number of cases studied is limited, the data indicate that the tendency is toward a macrocytic, hypochromic type of anemia Past experience with the Pijper halometer permits us to conclude that 8.0 microns is the extreme upper limit of normal for mean corpuscular diameter in this vicinity Our normal range is from 7.5 to 8.0 Thus it is clear that in the 4 cases

just mentioned the mean corpuscular diameter and the mean corpuscular volume are moderately increased, while the mean corpuscular hemoglobin concentration, in conformity with the color index, is slightly reduced.

The tendency to reduction of the color index and of the mean corpuscular hemoglobin concentration suggests that there is, in addition to a heightened destruction of erythrocytes, a disturbance in the formation of hemoglobin. In many other hemolytic anemias, for instance, that due to phenylhydrazine or distilled water, this is not the case, and in these the color index and hemoglobin concentration are high. One condition, however, is very similar, with respect not only to the size and hemoglobin content of the red blood cells but also to pigment metabolism. This is the anemia of lead poisoning, which is likewise characterized by increased destruction of blood with relative reduction of the hemoglobin content of the erythrocytes¹⁷. It is also of much interest that coproporphyrin III has been found to be excreted in the urine in cases of lead poisoning¹⁸ and after administration of sulfanilamide¹⁹. This porphyrin, which corresponds in configuration to the hemoglobin series, may possibly owe its formation to a disturbed hemoglobin synthesis.

Our data as regards urinary excretion of coproporphyrin are limited to 4 of the cases of group 1²⁰. While the porphyrin determinations in these cases have not yielded information from which definite conclusions can be drawn, they are at least of value in revealing that the effect of sulfanilamide on porphyrin metabolism is by no means a constant one. In case 1 it is seen that a questionably significant rise of urinary porphyrin followed the administration of sulfanilamide and that a marked drop had occurred two days after its discontinuance. This drop was associated with marked clinical improvement, and the patient has remained in good health. The quantitative determination of urinary porphyrin includes the isomeric coproporphyrins I and III but does not

17 Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, P. Lead Poisoning, *Medicine* **4** 1, 1925. Hirschfeld, H. Symptomatische Blutveränderungen, in Schittenhelm, A. *Handbuch der Krankheiten des Blutes und der blutbildenden Organe*, Berlin, Julius Springer, 1925, vol. 1, p. 189.

18 Grotepass, W. Zur Kenntnis des in Harn auftretenden Porphyrins bei Bleivergiftung, *Ztschr. f. physiol. Chem.* **205** 193, 1932. Fischer, H., and Duesberg, R. Ueber Porphyrine bei klinischer und experimenteller Porphyrinurie, *Arch. f. exper. Path. u. Pharmacol.* **166** 95, 1932. Watson, C. J. Concerning the Naturally Occurring Porphyrins. IV. The Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, *J. Clin. Investigation* **15** 327, 1936.

19 Rimington, C. Porphyrinuria Following Sulfanilamide. Sulfanilamide Dermatitis, *Lancet* **1** 770, 1938.

20 Further study of the effect of sulfanilamide on porphyrin metabolism is in progress.

distinguish between them. It is quite possible that the mild increase in porphyrin noted even before administration of sulfanilamide was due to excessive excretion of coproporphyrin I related to mild hepatic dysfunction²¹. Disturbance of hepatic function has been noted in cases of brucellosis²².

In case 3 (chart 3) a definite although not marked increase in urinary coproporphyrin is noted, occurring soon after sulfanilamide therapy was commenced. This is of questionable significance, however, since the twenty-four hour amount soon decreased to the level observed before the drug was given. In case 4 (chart 4), an instance of severe rheumatoid arthritis, the value was considerably elevated before treatment with sulfanilamide was commenced. Shortly thereafter a marked further increase was noted, and associated with this a toxic rash of morbilliform type appeared. The use of the drug was discontinued, but the coproporphyrin excretion remained elevated. At the same time the urobilinogen content of the feces returned to normal. It is of interest that no elevation of the serum bilirubin and only a mild increase of the urine urobilinogen occurred in this case. A distinct increase in the rate of blood destruction was noted, however. In case 5 (chart 5) no significant variations in the level of urinary coproporphyrin were noted before, during or after therapy. It may be of importance that in this case relatively little effect was noted on either hemoglobin metabolism or hepatic function.

Hepatic Function—As has been noted, jaundice has been observed only in the group of patients receiving sulfanilamide. We cannot exclude the possible occurrence of slight elevation of the serum bilirubin in some of the sulfapyridine-treated patients, as we have made frequent determinations in but 2 cases (7 and 8 in group 1). In neither of these cases was there any increase of serum bilirubin, although relatively large doses of the drug were given and blood levels of 10 to 12 mg per hundred cubic centimeters were attained. In contrast to cases 7 and 8 are cases 1 to 6. Significant elevation of the level of serum bilirubin was noted in 5 of these (all except case 4). In case 8 (chart 5), during administration of sulfapyridine, a sustained level of 8 to 12 mg per hundred cubic centimeters of blood sulfapyridine was attained without elevation of the serum bilirubin. After an interval, as is shown in chart 5, sulfanilamide was administered, and the serum bilirubin mounted to 1.49 mg per hundred cubic centimeters.

21 Watson, C. J. The Porphyrins and Their Relation to Disease. Porphyrin, in Christian, H. A. Oxford Medicine, New York, Oxford University Press, 1938, vol. 4, chap. 9-a, p. 228.

22 Mettier, S. R., and Kerr, W. J. Hepatitis and Cholecystitis in the Course of Brucella Infection. Report of a Case, Arch. Int. Med. 54:702 (Nov.) 1934.

While further investigation is necessary to determine whether sulfapyridine causes jaundice, the present observations reveal that the condition is at least much less common after its use than after the use of sulfanilamide^{22a}

We regard jaundice as an evidence of at least relative dysfunction of the liver. Just as in certain cases of familiar hemolytic anemia the liver remains equal to the task of excreting the increased amount of bilirubin in the bile and jaundice fails to appear,¹⁶ sulfanilamide or sulfapyridine may cause increased hemolysis of considerable degree, with increase of urobilinogen in the feces but without elevation of the serum bilirubin. This is seen in cases 4, 7 and 8. In the 16 cases in which jaundice was noted after sulfanilamide, the van den Bergh reaction was of the direct type, often biphasic. Since there was no question of mechanical obstruction in these instances, the direct van den Bergh reaction may be regarded as concrete evidence of regurgitation jaundice due to damage to the liver.

The regular and often marked elevation of the urobilinogen content of the urine after sulfanilamide therapy is regarded as further evidence of parenchymal damage to the liver. It is clear (chart 5) that even extreme urobilinogenuria may occur without any regurgitation jaundice and even without hepatocellular dysfunction as regards bilirubin excretion (case 8). Although there can be no doubt that increased hemolysis, with resultant increased formation of urobilinogen in the bowel, predisposes to urobilinogenuria, it is believed, as has been stated in detail elsewhere,¹² that some degree of dysfunction of the liver is necessary to the appearance of appreciable increases of urobilinogen in the urine. In 2 cases (3 and 5) significant elevation of the level of serum bilirubin was noted without urobilinogenuria. The reason for this is not clear, but it can only be assumed that certain livers dispose of urobilinogen more readily than of bilirubin. The possibility of a disturbance in the absorption of urobilinogen from the bowel must also be considered.

Fever, either natural or artificial, does not appear to be correlated in any way with elevation of the bilirubin content of the serum or of the urobilinogen content of the urine. In case 2 the values for urine urobilinogen were somewhat higher during the second period, in which sulfanilamide and artificial fever were combined. It is doubtful, however, that the difference between the first and the second period is significant when it is considered that there are many other causes of spontaneous fluctuation in the degree of urobilinogenuria.²³ In case 3

22a Only 1 instance of jaundice following administration of sulfapyridine has been observed during the nine months since this paper was written. In this period, approximately 150 additional patients have been treated with sulfapyridine.

23 Watson, footnotes 6 *b* and *c* and 12.

no increase occurred in spite of repeated fever treatments plus administration of sulfanilamide

Although the degree of fever alone is not correlated with evidence of dysfunction of the liver, we have been impressed by the greater frequency with which jaundice and urobilinogenuria have been noted in patients who might be classified as relatively very ill or toxic when given sulfanilamide, as contrasted with patients who were relatively nontoxic. The only instance of outspoken jaundice in group 1 was in case 6 (chart 1), the patient was in a very serious condition and showed slight elevation of the serum bilirubin when administration of sulfanilamide was commenced. A similar sequence of events is noted in case 16 of group 2. Of the 16 patients in group 2 in whom mild to marked jaundice was observed, all were very ill or toxic when administration of the drug was begun. It is noteworthy that extreme degrees of jaundice were noted in cases 11 and 12 (table 1), in both of which sulfanilamide was placed directly in the peritoneal cavity at the time of operation. In these cases it is safe to conclude that hepatic damage of some degree had already occurred before operation, since in both cases there was undoubtedly drainage of damaging substances directly into the portal circulation. Icterus appeared only postoperatively, and the intensity was such that there could be little doubt that sulfanilamide had been an important factor in its development. We consider it unlikely, however, that similarly intense icterus would have developed in the absence of the primary disease. Thus, in case 28 of group 2 (table 1), it may be noted that jaundice did not appear, although an equally large amount of sulfanilamide was placed in the peritoneal cavity and relatively large amounts of the drug were given intravenously after operation. Two differences may explain the absence of jaundice in this case in contrast to the deep jaundice in cases 11 and 12. The first is that the blood level of sulfanilamide did not become elevated to a marked degree as it did in cases 11 and 12. The second difference was that the patients in the latter cases were much more toxic and their infection was not as well localized.

In the medical service sulfanilamide has been given in but 1 case in which distinct jaundice was noted prior to therapy. This was case 20. As is noted in table 1, sulfanilamide had been given to this patient during two four day periods before admission to the University Hospital. At the time of admission the patient was comatose and distinctly jaundiced. The icterus index was 32. Supportive measures were of no avail, and since it appeared evident that the patient would die of hemolytic streptococcus septicemia, more sulfanilamide was given, starting with an initial amount of 4 Gm. It is seen that the icterus index increased to 68 within forty-eight hours. Death occurred on the sixth

day of hospitalization. The relative importance of the infection and of the sulfanilamide in the production of jaundice in this case cannot be determined.

We have not observed any strict correlation of the data for serum bilirubin or urine urobilinogen with those for the free or total blood sulfanilamide or sulfapyridine levels. The values noted in case 3 are of interest in this respect. It is seen that the serum bilirubin rose to 2.17 mg per hundred cubic centimeters at the end of the first course of therapy. The blood sulfanilamide level had now fallen to 7.7 mg per hundred cubic centimeters from a peak of 17.4 mg nine days earlier, at which time the serum bilirubin was at a normal level. A distinct although slight rise of the urine urobilinogen occurred in this first period. During the second period, in which the patient was also subjected repeatedly to artificial fever, the blood sulfanilamide level rose to 23 mg per hundred cubic centimeters, but there was no increase of either serum bilirubin or urine urobilinogen.

In cases 10 and 26, small doses of sulfanilamide used in treating infections of the urinary tract appeared to exert no influence on the function of the liver. In neither case did jaundice or urobilinogenuria appear. We have not observed jaundice in any adult receiving less than 3 Gm of sulfanilamide per day, and increases of urinary urobilinogen have not been observed in such instances. It appears, therefore, that there may be some correlation with the amount of the drug given. Our results indicate that when doses of 4 to 8 Gm of sulfanilamide are given daily, some disturbance of hepatic function may be expected in most instances. The degree of disturbance probably depends on two factors: (1) individual variation in susceptibility to the drug and (2) the toxicity of the underlying disease, particularly the extent of its toxic effect on the liver.

CONCLUSIONS

- 1 Sulfanilamide in customary therapeutic doses usually causes acceleration of the metabolism of hemoglobin characterized by an increase of urobilinogen in the feces and a varying increase in the reticulocyte percentage. The most marked acceleration of hemoglobin metabolism is represented by the unusual cases in which outspoken hemolytic anemia occurs. This condition is therefore to be regarded as a much more marked degree of a usual toxic effect of the drug. Limited data indicate that sulfapyridine has the same effect as sulfanilamide on hemoglobin metabolism.

- 2 The occurrence of macrocytic or normocytic, mildly hypochromic anemia after administration of sulfanilamide or sulfapyridine indicates a disturbance in hemoglobin formation in addition to increased hemolysis.

3 In many persons the administration of sulfanilamide in the usual doses is followed by some evidence of dysfunction of the liver, such as urobilinogenuria, elevation of the serum bilirubin or outspoken jaundice. The last-mentioned condition is in part of the regurgitation type, as is evidenced by the frequent occurrence of a direct van den Bergh reaction. Sixteen cases of jaundice following sulfanilamide therapy have been encountered. But 1 instance has been noted in which jaundice followed use of sulfapyridine.^{22a} Administration of sulfapyridine has not resulted in any elevation of the serum bilirubin in 2 cases in which frequent determinations were made before, during and after administration of the drug. This is in contrast with the results in the group treated with sulfanilamide, in which significant elevation of the serum bilirubin was usual. Although the data on sulfapyridine are as yet too limited to permit definite conclusions, there is reason to believe that this drug may not be as disturbing to hepatic function as is sulfanilamide.

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Progress in Internal Medicine

LIVER AND BILIARY TRACT

A REVIEW FOR 1939

CARL H. GREENE, M.D., PH.D.

NEW YORK

AND

ELLISTON FARRELL, M.D.

BROOKLYN

PHYSIOLOGY OF THE BILE ACIDS

The bile acids are formed in the liver and may be considered the specific secretion of that organ. In consequence they are recognized as the most characteristic constituent of the bile. The literature relative to the metabolism of the bile acids has been summarized in the past by Stadelmann¹ and Whipple⁴ and most recently by Sobotka⁵. The recent literature on the chemistry of the bile acids was reviewed in 1936 (Greene⁶). Since the last two reports there has been increasing progress in this field. These studies may be summarized under several different headings: (1) experimental and clinical studies on the effect of diet on the secretion of bile, (2) the postoperative concentration of bile salts in human bile, (3) the excretion of intravenously injected cholates, (4) experimental and clinical studies on the effect of the administration of bile salts on the composition of bile, and (5) the therapeutic use of bile salt preparations.

The first reported observations on the volume and composition of the bile were made on patients in whom biliary fistulas had developed spon-

From the Clinic for the Study of Diseases of the Liver and Biliary Tract of the Department of Medicine and the Department of Surgery, New York Post-Graduate Medical School and Hospital, New York, and the Long Island College Division of the Kings County Hospital, Brooklyn.

1 Stadelmann, E. *Der Icterus und seine verschiedenen Formen nebst Beiträgen zur Physiologie und Pathologie der Gallensecretion*, Stuttgart, Ferdinand Enke, 1891.

2 and 3 Footnotes have been deleted.

4 Whipple, G. H. *The Origin and Significance of the Constituents of the Bile*, *Physiol. Rev.* **2**: 440-459, 1932.

5 Sobotka, H. *Physiological Chemistry of the Bile*, Baltimore, Williams & Wilkins Company, 1937.

6 Greene, C. H. *Liver and Biliary Tract. A Review of Certain Recent Contributions*, *Arch. Int. Med.* **57**: 1039-1054 (May) 1936.

taneously, usually as a result of external rupture of an abscess. A hundred years later the development of modern surgical methods of cholecystotomy and cholecystectomy permitted the study of factors affecting the volume and composition of human bile.

A bile fistula in a patient is not necessarily complete. There usually is associated disease of the liver or of the bile ducts, and it is difficult to regulate the diet and activity of the patient so as to obtain unequivocal results.

Such observations led Douglas,⁷ in 1817, and Bidder and Schmidt,⁸ in 1852, to the experimental production and study of biliary fistulas in animals. The early bile fistulas were complicated by the presence of the gallbladder, which may influence markedly the character of the bile drainage. Even when the gallbladder was removed and associated infection avoided, McMaster, Brown and Rous⁹ found marked and inexplicable variation in the daily output of bile.

Kocour and Ivy¹⁰ report that by further improvements in the detail of the methods of collecting bile they have been able to obtain consistent and reproducible results under similar experimental conditions. They used female dogs and prepared their bile fistulas by a modification of the method of Rous and McMaster.¹¹ During the experimental period continuous suction was applied to the fistula tube to prevent possible blocking. Using this method, Kocour and Ivy¹⁰ report that under similar experimental conditions the secretion of bile did not vary more than 4 per cent. They report that the volume of bile secreted by the liver under controlled experimental conditions is as constant as the secretion of any of the external secretory glands.

The secretion of bile varied with the diet and the amount of bile returned to the intestine. It was lowest (6 to 10 cc per kilogram per day) when the animal was fasting and there was no return of bile. On a mixed diet but without return of bile the output ranged from 13 to 18 cc

7 Douglas, L. Operations on the Liver and Other Secreting Glands, *M Repository* **4** 283-286, 1817.

8 Bidder, F, and Schmidt, C. *Die Verdauungssäfte und des Stoffwechsel*, Leipzig, G. A. Reyher, 1852.

9 McMaster, P. D., Brown, G. O., and Rous, P. Studies of the Total Bile I. The Effects of Operation, Exercise, Hot Weather, Relief of Obstruction, Inter-current Disease, and Other Normal and Pathological Influences, *J Exper Med* **37** 395-420, 1923.

10 Kocour, E. J., and Ivy, A. C. The Effect of Certain Foods on Bile Volume Output Recorded in the Dog by a Quantitative Method, *Am J Physiol* **122** 325-346, 1938.

11 Rous, P., and McMaster, P. D. A Method for the Permanent Sterile Drainage of Intra-Abdominal Ducts, as Applied to the Common Duct, *J Exper Med* **37** 11-19, 1923.

per kilogram per day, whereas on a mixed diet with a return of a standard amount of bile to the intestine it ranged from 24 to 27 cc per kilogram per day

Hot weather had no effect on the volume of the bile when the appetite was unimpaired. The drinking of water or the intravenous injection of 0.5 per cent sodium chloride solution likewise was without effect.

Mixed diet stimulated the output of bile, and meat was the most potent food, whether taken alone or added to a mixed diet. Beef liver was more effective than muscle or beef heart. Olive oil increased the output of bile in fasting dogs, but this effect was not observed when the dose was repeated or when the oil was added to a mixed diet. Dextrose administered to a fasting animal produced a 20 to 30 per cent decrease in the output of bile. When dextrose was added to a mixed diet, there was no characteristic change in the secretion of bile. However, if the secretion of the liver was stimulated by the giving of bile, and dextrose was then injected intravenously, the secretion of bile was increased.

The most marked increases in the volume of the bile followed the administration of bile. Because of greater concentration of bile acids, bile from the gallbladder was a stronger stimulant than bile from the hepatic ducts.

Schmidt, Beazell, Berman, Ivy and Atkinson,¹² continued these studies, but in addition to measuring the volume of the bile they determined the daily excretion of bile acids as cholates, cholesterol and pigment. Under standard conditions without return of the excreted bile, the output of these various biliary constituents was quite constant. The daily output of bile acids varied from 1.2 to 1.9 Gm, but when all the bile was returned to the duodenum the output was increased to 6.5 to 9.0 Gm. From this, Schmidt and his associates concluded that while there is an active enterohepatic circulation of bile acids, from 10 to 15 per cent is lost on each circuit. This loss is compensated by the bile formed endogenously and from the diet, and the output is more or less constant.

Atropine and acetylbetamethylcholine prevented the increase in volume and cholates that normally followed a mixed meal.

Companion studies in patients with bile fistulas have been reported by Zuckerman, Kogut and Jacobi,¹³ who observed that in a patient with

12 Schmidt, C. R., Beazell, J. M., Berman, A. L., Ivy, A. C., and Atkinson, A. J. Studies on the Secretion of Bile, *Am J Physiol* **126** 120-135, 1939.

13 Zuckerman, I. C., Kogut, B., and Jacobi, M. Studies in Human Biliary Physiology. I. Fasting Rate and Quantity of Bile Secretion, *Am J Digest Dis* **6** 183-185, 1939. Jacobi, M., Zuckerman, I. C., and Kogut, B. Studies in Human Biliary Physiology. II. The Effect of Food Factors and Orally Administered Bile on the Rate and Quantity of Bile Secretion, *ibid* **6** 270-274, 1939.

an apparently normal liver the hourly rate of flow was fairly regular except for slight diminution during the night. The rate of secretion was not affected by changes in the intake of water. When carbohydrate was fed, there was no increase in the volume of bile. A mixed hospital diet or a diet high in fat produced a moderate increase in the output of bile, but the most marked change followed the use of a diet high in protein. The oral administration of bile produced a further increase in the output of bile that was in most instances independent of the food. When a maximal choleresis had been produced by a high protein diet, bile was less effective in increasing this response.

The insertion of a T tube and drainage of the common bile duct permit the study of human bile. During the past ten years there has been an increasing number of such reports. For the most part these reports have been concerned with the secretion of bile salts by the liver during the first week or two after the insertion of the drainage tube.¹⁴ Greene, Hotz, Carter and Twiss,¹⁵ who have made the most recent study of this problem, point out that there is general agreement that when the patient has had no evidence of hepatic disease or the latter is minimal there is a temporary reduction in the concentration of cholates in the bile followed after two to three days by a progressive return to normal levels. This drop apparently is due to the individual or combined effects of a variety

14 (a) Greene, C. H., Walters, W., and Frederickson, C. H. The Composition of the Bile Following the Relief of Biliary Obstruction, *J. Clin. Investigation* **9** 295-310, 1930. (b) Walters, W., Greene, C. H., and Frederickson, C. H. The Composition of the Bile Following the Relief of Biliary Obstruction. Report of a Series of Illustrative Cases, *Ann. Surg.* **91** 686-693, 1930. (c) Sterner, R. F., Bartle, H. J., and Lyon, B. B. V. Chologogue Effect of Intravenous Injection of Sodium Dehydrocholate, *Am. J. M. Sc.* **182** 822-839, 1931. (d) Ravdin, I. S., Johnston, C. G., Riegel, C., and Wright, S. L. A Study of Human Liver Bile After Release of Common Duct Obstruction, *J. Clin. Investigation* **12** 659-672, 1933. (e) Breusch, F., and Johnston, C. G. Zum Verschwinden und Wiedererscheinen der Gallensauren in der Galle bei vorübergehendem Choledochusverschluss, *Klin. Wchnschr.* **13** 1856-1857, 1934. (f) Kohlstaedt, K. G., and Helmer, O. M. The Effect of Oral Administration of Bile Salts on Composition of Human Fistula Bile, *Am. J. Digest. Dis. & Nutrition* **4** 306-312, 1937. (g) Doubilet, H. Hepatic Excretion in Man of the Various Bile Acids Following Their Oral Administration, *Proc. Soc. Exper. Biol. & Med.* **36** 50-52, 1937. (h) Gray, H. K., Butsch, W. L., and McGowan, J. M. Effect of Biliary Operations on the Liver. Their Relation to the Concentration of Bile Acids in the Bile, *Arch. Surg.* **37** 609-618 (Oct.) 1938. (i) Gray, H. K., McGowan, J. M., Nettrour, W. S., and Bollman, J. L. Hepatic Damage in Biliary Disease. Its Relation to the Concentration of Bile Acids in the Bile, *ibid.* **37** 790-799 (Nov.) 1938.

15 Greene, C. H., Hotz, R., Carter, R. F., and Twiss, J. R. The Post-Operative Concentration of Bile Salts in Human Bile, *Am. J. Surg.*, 1940, to be published.

of different factors. The anesthetic agent and the duration of anesthesia, the local as well as the constitutional effects of the operative trauma, the degree of preoperative biliary obstructive and hydrohepatosis and the like factors must all be taken into consideration in interpreting results.

After the initial drop the concentration of cholates in the bile returns toward the normal. The rapidity of this return and the maximal concentration attained during the period of observation are in general inversely proportional to the degree of hepatic damage. The hepatic damage may be evidenced by structural changes as cirrhosis, but Greene, Hotz, Carter and Twiss point out that functional insufficiency may be present without gross pathologic changes. They present evidence that such factors as systemic infection, fever, cholangitis, depletion of bile salts from prolonged drainage or an inadequate supply of carbohydrate will reduce the concentration of cholates in the bile, presumably as a result of functional disturbance. They confirm the report of Greene, Walters and Friedrickson^{14a} that the continued failure of the liver to secrete bile acids is evidence of severe functional disturbance and so may be of serious prognostic import.

These studies of the postoperative changes in the concentration of bile salt in the bile are important, for they indicate the multiplicity of factors which affect the functional activity of the liver. The multiplicity of these factors, however, greatly increase the difficulty of determining the ones responsible for the changes in any individual case.

Bile acids, whether administered by mouth or intravenously, are rapidly and quantitatively excreted in the bile. This was suggested by the early studies of Stadelmann,¹ Kuhne,¹⁶ and Huppert.¹⁷ Greene and Snell¹⁸ studied the process in more detail and emphasized the rapidity with which intravenously injected bile acids disappeared from the blood stream. The time required for their removal varied with the dose but even with maximal doses the greater part of the injected bile acids were removed from the blood within thirty minutes. Excretion in the bile likewise was rapid but showed a definite delay, for the peak of the excretion did not come until after the blood had returned to normal. This problem has been studied further by Snell, Greene and

16 Kuhne, W. Beitrage zur Lehre vom Icterus, *Virchows Arch f path Anat* **14** 310-356, 1858.

17 Huppert, H. Ueber das Schicksal der Gallensauren im Icterus, *Arch d Heilk* **5** 236-256, 1864.

18 Greene, C. H., and Snell, A. M. Studies in the Metabolism of the Bile. II. The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile or Its Constituents, *J Biol Chem* **78** 691-713, 1928.

Rowntree,¹⁹ Bollman and Mann,²⁰ Chabrol, Cottet and Sallet,²¹ and Lichtman,²² with similar results. More recently it has been reinvestigated by Josephson, Jungner and Rydin,²³ who studied the fate of injected sodium cholate. They used the method of Josephson and Jungner,²⁴ which permitted determination of both free cholic acid and conjugated bile acid. They found, in confirmation of the earlier studies, that intravenously injected sodium cholate usually was removed from the blood stream in about thirty minutes. The bile acids were less rapidly excreted in the bile, but, interestingly enough, during the first half hour after the injection they were excreted preponderately as free cholic acid, while thereafter a rapidly increasing proportion were conjugated before excretion.

Jungner, Rydin and Josephson,²⁵ continued this study in experimental jaundice in animals. They found, as Snell, Greene and Rowntree,¹⁹ Bollman and Mann²⁰ and others did, that the concentration of bile acids in the blood was increased after ligation of the common bile duct. They confirmed the report of Snell, Greene and Rowntree that injected cholates were removed from the blood stream less rapidly than normally. This delay in excretion, however, was much more marked in cases of toxic hepatitis produced by administration of phosphorus or carbon tetrachloride. Their experiments were extended to patients, and Josephson and Larsson²⁶ found that sodium cholate injected intravenously in man rapidly disappears from the blood and is rapidly and quantitatively excreted by the liver into the bile.

The intravenous injection of a solution of sodium cholate produced a greater rise in the cholic acid content of the blood in patients with

19 Snell, A. M., Greene, C. H., and Rowntree, L. G. Diseases of the Liver. Further Studies in Experimental Obstructive Jaundice, *Arch. Int. Med.* **40** 471-487 (Oct.) 1927.

20 Bollman, J. L., and Mann, F. C. The Influence of the Liver in the Formation and Destruction of Bile Salts, *Am. J. Physiol.* **116** 214-224, 1936.

21 Chabrol, E., Cottet, J., and Sallet, J. Recherches comparatives sur le pouvoir de concentration du foie et du rein vis-à-vis de l'acide cholalique, *Compt. rend. Soc. de biol.* **122** 184-186, 1936.

22 Lichtman, S. The Blood Clearance and Renal Excretion of Bile Acids Following the Intravenous Injection of Cholic and Desoxycholic Acids, *Am. J. Physiol.* **117** 665-671, 1936.

23 Josephson, B., Jungner, G., and Rydin, A. Elimination of Cholic Acids. I. In Healthy Animals, *Acta med. Scandinav.* **97** 237-253, 1938.

24 Josephson, B., and Jungner, G. A Comparison of Some Methods for the Determination of Bile Acids in Bile and the Proportion Between the Different Acids, *Biochem. J.* **30** 1953-1959, 1936.

25 Jungner, G., Rydin, A., and Josephson, B. Elimination of Cholic Acids. II. In Experimental Jaundice, *Acta med. Scandinav.* **97** 254-264, 1938.

26 Josephson, B., and Larsson, H. Elimination of Cholic Acids. III. In Man, *Acta med. Scandinav.* **99** 140-146, 1939.

jaundice than in normal persons (Josephson²⁷) Patients with obstructive jaundice showed a moderately rapid fall in the cholic acid content of the blood, and the initial level usually was regained at the end of the hour In patients with acute hepatitis the fall of the blood levels was greatly delayed, and these levels were still elevated at the end of an hour The tables show considerable overlapping between the different groups, but Josephson recommends the test as valuable in arriving at a differential diagnosis between these two kinds of jaundice

The study of the effect of bile salts and of various therapeutic agents on the volume and composition of the bile was extended by Schmidt, Beazell, Atkinson and Ivy²⁸ The various types of response obtained make it desirable for the physician as well as the physiologist to distinguish between three related effects on the liver and biliary tract

Cholagogues stimulate the evacuation of the gallbladder and increase the flow of bile into the intestine but do not increase the rate of secretion by the liver

Hydrocholeretics increase the volume of the bile but do not stimulate the secretion of biliary constituents

Choleretics produce an increased flow of bile and an increased elimination of biliary constituents

Schmidt, Beazell, Atkinson and Ivy²⁸ studied the effect of a number of drugs on the secretion of bile Mild mercurous chloride has long had a reputation based on its reputed clinical effectiveness in cases of "biliousness" or of "torpid liver" This has not been confirmed by previous experimental work In the present study, this drug in doses of 100 mg had no effect on either the volume or the constituents of the bile Ammonium chloride, urea, calcium gluconate, mucin, chondroitin and sulfanilamide were tested and all found to be without significant effect on the secretion of bile The authors found, as have other investigators, that sulfanilamide was eliminated in the bile in concentrations that have been reported to be bacteriostatic

Acetylsalicylic acid increased the volume of the bile by approximately 59 per cent but reduced the excretion of cholates slightly

Oxidized unconjugated bile acid derivatives, such as the proprietary preparations decholin and ketochol, acted as hydrocholeretics, for they more than doubled the volume of the bile but reduced the excretion of cholates by approximately a third

27 Josephson, B Elimination of Cholic Acids IV In Patients with Liver Disease, *J Clin Investigation* **18** 343-350, 1939

28 Schmidt, C R, Beazell, J M, Atkinson, A J, and Ivy, A C The Effect of Therapeutic Agents on the Volume and the Constituents of Bile, *Am J Digest Dis* **5** 613-617, 1938

Conjugated ketocholanic acids (such as are contained in the proprietary preparation dechacid) had a moderate choleietic action, for the volume of the bile was increased. The excretion of cholates was not changed, but because of the excretion of the administered ketocholanic acids the total bile acid output was increased. These results indicate a specific action of conjugated bile acids which is not shown by the unconjugated preparation, but the authors did not explain the reason for this difference in the two preparations.

Normally occurring conjugated cholic acids (such as are contained in the proprietary preparation bilron) and dog bile were the most satisfactory choleietics, for they produced both an increased flow of bile and an increased excretion of bile salts. In the latter case, it must be remembered that the increase was due to elimination of administered cholates and not to increased synthesis of bile acids.

Effect of Certain Drugs on the Secretion and the Constituents of Bile

	Percental Change Over Control Period			
	Volume	Cholates	Pigment	Cholesterol
Bilron*	+74	+126	+39	+110
Dechacid*	+50	+4	-17	+50
Ketochol†	+144	-28	+35	+80
Decholin†	+125	-36	-17	-45
Acetylsalicylic acid	+59	-4	+7	+33
Sulfanilamide	+4	-5	+8	-10
Mild mercurous chloride U S P	0	+8	+16	-33
Linseed oil U S P	+16	+10	+27	+37

* Conjugated bile acids of ox bile

† Oxidized unconjugated bile acids

Doubilet²⁹ also reported a study of the hepatic excretion in dogs following oral administration of various bile acids. When cholic acid was administered, there was a marked increase in the excretion of cholic acid and some increase in that of desoxycholic acid. The administration of desoxycholate increased the excretion of that salt but depressed the excretion of cholate. Doubilet measured the efficiency of the liver by the maximum excretion of bile acids in the smallest volume of bile. When this index was used, the order of decreasing efficiency in the dog was dog bile, ox bile, glycocholic acid, cholic acid, desoxycholic acid and dehydrocholic acid.

Riegel, Ravdin and Prushankin,³⁰ studied the effect of dehydrocholic acid in 5 dogs and report that in all there was an increase in the volume

29 Doubilet, H. Hepatic Excretion in the Dog Following Oral Administration of Various Bile Acids, *Proc Soc Exper Biol & Med* **36** 687-690, 1937

30 Riegel, C, Ravdin, I S, and Prushankin, M. Effect of Sodium Dehydrocholate (Decholin) on Bile Salt, Chloride and Cholesterol of Bile in Dogs, *Proc Soc Exper Biol & Med* **41** 392-395, 1939

of bile, with 71 per cent as the average. There was little change in the excretion of cholesterol but a slight (20 per cent) increase in the excretion of cholates. The last finding is at variance with the results of Doubilet²⁹ and of Schmidt and his co-workers²⁸. While there was a slight change in the cholates, the more marked increase in the volume of bile still seems to classify the response as hydrocholeretic.

The rational therapeutic use of bile salts depends on an understanding of their functions and activities in the body. These have been discussed in detail in a recent article by Ivy and Berman³¹. These investigators point out that

- 1 Bile salts promote the formation of bile. They increase the volume of bile and the output of cholesterol and bile salts but do not affect the excretion of pigment. All, or all but about 10 per cent, of administered natural bile salts are reexcreted in the bile.

- 2 Bile salts, by keeping fatty acids in solution, may act to prevent precipitation of cholesterol and fatty acids in the gallbladder.

- 3 Natural bile salts aid in the digestion and absorption of fats.

- 4 Natural bile salts facilitate the absorption of iron and calcium and are necessary for the absorption of carotene, of cholesterol and of vitamins D, E and K.

- 5 Bile salts administered orally have a laxative action.

- 6 Bile salts are said to play a role in detoxifying bacterial toxins in the intestinal tract.

- 7 Bile salts may affect the storage of glycogen by the liver.

Ivy and Berman³¹ discuss the therapeutic use of bile salts under several headings. They point out that in the absence of bile salts in the intestine oral administration of bile salts is indicated to improve digestion and absorption. The profound digestive and nutritional disturbances observable in patients with complete biliary fistulas or with complete biliary obstruction and the symptomatic relief obtained from the administration of bile salts in adequate dosage are evidence for the truth of this recommendation. The importance of giving bile salts as well as vitamin K in the preoperative preparation of jaundiced patients is recognized. The possible harmfulness of the administration of bile salts to a patient with complete biliary obstruction is considered by Ivy and Berman. They point out that clinical experience has demonstrated that oral administration for short periods of time is without evident deleterious effects. They obtained similar results in a few prolonged animal experiments. The earlier studies of Brakefield and

³¹ Ivy, A. C., and Berman, A. L. The Rationale of Bile Salt Therapy in Biliary Tract Disease. *Minnesota Med* **22** 815-820, 1939.

Schmidt³² and the more recent ones of Mann and Bollman, showing that in dogs with obstructive jaundice there is rapid excretion of orally administered bile acids in the urine, may explain the apparent absence of toxic effects in such patients

We wish to emphasize the difference between the administration of bile salts in adequate dosage in the presence of a demonstrated deficiency of bile in the intestine and the widespread popular use of bile-containing pills for the relief of "biliousness" or a "sluggish liver." Too often the condition which the patients seek to correct is one of constipation, and the therapeutic benefit experienced is due to the presence in the preparation of active cathartics, such as aloin, phenolphthalein and the like, and not to the minute amounts of bile salts which are included

In disease of the biliary tract without acute hepatitis, bile salts are administered to flush the biliary passages with a copious flow of bile of low viscosity. This use of bile salts is rational so far as the bile ducts are concerned, for, as Ivy and Berman indicate, a brisk flow of bile through the hepatic ducts would tend to prevent ascent of infection. We agree as to the value of the administration of bile salts as a post-operative measure in cases in which T tube drainage of an infected common bile duct has been instituted. Because of the hydrocholeretic effect of bile salts, it is possible that the derivatives of oxidized bile acids, such as ketochol and decholin, are preferable to the natural bile acids in this condition. Flushing of the ducts is less certain in the patient who has not been operated on, for theoretically a hypertonic sphincter of Oddi might prevent a free flow of bile. However, Ivy and Goldman³³ point out that spasm of the sphincter is less readily produced if the liver is secreting freely

Flushing of the gallbladder is a different problem from flushing of the bile ducts, and Ivy and Berman point out that the extent to which the administration of bile will change the chemical constitution of bile in the gallbladder and flush out the gallbladder is uncertain. It also must be remembered that in cases of either acute or chronic cholecystitis in which the gallbladder does not fill, a copious flow of bile could accomplish only a flushing of the bile ducts

In the presence of disease of the biliary tract and acute hepatitis the use of bile salts has been implied to be of benefit by a number of clinical observers. Ivy and Berman insist that until more unequivocal observations become available they doubt the wisdom of bile salt therapy in

32 Brakefield, J. L., and Schmidt, C. L. A. Studies on the Synthesis and Elimination of Certain Bile Components in Obstructive Jaundice, *J. Biol. Chem.* **67** 523, 1926

33 Ivy, A. C., and Goldman, L. Physiology of the Biliary Tract, *J. A. M. A.* **113** 2413-2417 (Dec. 30) 1939

such conditions except for the purpose of improving intestinal absorption. The previously reported studies have shown that the presence of cholangitis reduces or abolishes the choleretic effect of bile salt preparations and that injected bile salts are not removed from the blood stream at the normal rate. We have been informed of a case of possible acute yellow atrophy following the intravenous administration of a preparation of oxidized bile salts. Under these conditions we wish to second this plea for caution in the therapeutic use of bile salts except when it can be shown that there are specific scientific indications for such use.

LEPTOSPIROSIS ICTEROHAEMORRHAGICA

Leptospirosis icterohaemorrhagica (Weil's disease, spirochetel jaundice) is an infection not of the liver alone but of all the organs of the body. Jaundice may be present, but it occurs in not more than 60 or 65 per cent of the serologically or bacteriologically proved cases.³⁴ Warrant for the consideration of this systemic infection in a review of the literature on diseases of the liver and biliary tract is derived partly from the traditional association of icterus with Weil's disease, which is reflected in the deceptive but much used synonym "spirochetel jaundice," and partly from the need for considering Weil's disease in the differential diagnosis of hepatitis.

The first adequate description of the clinical syndrome was formulated by Adolph Weil,³⁵ soon followed by Fiedler.³⁶ This was some three decades before the discovery of the causative agent, *Leptospira ictero-haemorrhagiae*, by Inada and others³⁷ in Japan and by Uhlenhuth and Fromme³⁸ in Germany. During the war of 1914-1918, knowledge of the infection grew by rapid stages out of a wide experience with the disease in soldiers. The extended reports in German³⁸ and in French³⁹

34 (a) Walch-Sorgdrager, B. Leptospiroses, Bull. Health Organ, League of Nations 8 143-386, 1939. (b) Davidson, L. S. P., and Smith, J. Weil's Disease in the North-East of Scotland. Account of One Hundred and Four Cases, Brit. M. J. 2 753-757, 1939.

35 Weil, A. Ueber eine eigenthumliche, mit Milztumor, Icterus und Nephritis einhergehende, acute Infectiouskrankheit, Deutsches Arch. f. klin. Med. 39 209-232, 1886.

36 Fiedler, A. Zur Weil'schen Krankheit, Deutsches Arch. f. klin. Med. 42 261-294, 1888.

37 Inada, R., Ido, Y., Hoki, R., Kaneko, R., and Ito, H. Etiology, Mode of Infection and Specific Therapy of Weil's Disease (*Spirochaetosis Icterohaemorrhagica*), J. Exper. Med. 23 377-402, 1916.

38 Uhlenhuth, P., and Fromme, W. Untersuchungen ueber die Aetiology, Immunitat und spezifische Behandlung der Weilschen Krankheit (*Icterus infectiosus*). Ztschr. f. Immunitatsforsch. u. exper. Therap. 25 317-480, 1916.

39 Martin, L., and Pettit, A. Spirochetose icterohemorrhagique, Paris, Masson & Cie, 1919.

which resulted are important source references, which have been supplemented but not supplanted by more recent monographs⁴⁰

On etiologic and clinical grounds, five general types of human leptospirosis can be differentiated^{34a} The type identified as Weil's disease, caused by invasion of *L. icterohaemorrhagiae*, is usually characterized by an abrupt onset, with fever, vomiting, great prostration and severe myalgia and, after a few days, by the appearance of jaundice

Jaundice, hepatomegaly, hemorrhagic manifestations, anemia, leukocytosis, albuminuria and retention of nitrogen are classic findings at the end of the first week The illness is commonly severe and is often prolonged by a febrile relapse in the third or fourth week Death terminates about 1 case in 9, hepatic, renal or cardiac damage may be the cause Without icterus, however, the prognosis is favorable, so that the fatality rate in Weil's disease with jaundice is perhaps 1 in 6

Weil's disease may follow an atypical course Meningeal symptoms sometimes predominate In an instance reported by Murgatroyd,⁴¹ evidence of meningeal involvement developed four months after the beginning of the illness, and leptospias were recovered from the cerebrospinal fluid and urine twenty-five and thirty-three weeks, respectively, after the onset Leptospirosis with marked signs of meningeal invasion has only recently been reported in the United States,⁴² but the condition should be considered in the differential diagnosis of meningitis in cases in which no organisms can be demonstrated in the cerebrospinal fluid by the usual staining and cultural techniques

A second type of leptospirosis found in Europe and America⁴³ is due not to *L. icterohaemorrhagiae* but to *Leptospira canicola*, the canine species Leptospirosis of this type is usually anicteric, and meningeal signs may be prominent The remaining three types of leptospiral infection include the swamp fever of central Europe, the seven day fever of Japan and other infections not found in America

In the transmission of leptospirosis *icterohaemorrhagica* the rat is an important agent Leptospias pathogenic for guinea pigs are shed in the urine of a variable proportion of these rodents In one recent

40 Uhlenhuth, P, and Fromme, W, in Kolle, W, Kraus, R, and Uhlenhuth, P Handbuch der pathogenen Mikroorganismen, ed 3, Jena, Gustav Fischer, 1930, vol 7, pt 1, pp 487-660 Walch-Sorgdiager^{11a}

41 Murgatroyd, F (a) Chronic Meningitis in Weil's Disease, Brit M J **1** 7-11, 1937, (b) Further Note on a Case of Chronic Leptospiral Meningitis, ibid **1** 445-446, 1939

42 Haschec, W, and Tobey, F J A Case of Weil's Disease, J A M A **113** 1319-1321 (Sept 30) 1939

43 Meyer, K F, Stewart-Anderson, B, and Eddie, B Canine Leptospirosis in the United States, J Am Vet M A **95** 710-729, 1939

survey J Smith⁴⁴ found such leptospiras in the kidneys of 27.3 per cent of 117 rats brought to the city hospital laboratory in Aberdeen, Scotland. There was a higher incidence of carriers among the full-grown rats than among the young animals. A positive seroreaction was present in the blood of 87.5 per cent of the rats from whose kidneys virulent leptospiras were isolated, but a positive reaction was also obtained in 24.7 per cent of the animals whose kidneys yielded none. The presence of immune bodies in the blood serum of rats has therefore no direct correlation with the carrier state.

Manual workers in trades which attract rats are particularly exposed to infection.⁴⁵ Fiedler³⁶ commented on the fact that 9 of the 12 victims observed by him were butchers. Miners in Scotland,⁴⁶ sewer workers in London⁴⁷ and Glasgow,⁴⁸ fish cutters in Aberdeen^{4b} and cane cutters in Australia⁴⁹ suffer from Weil's disease, and a British departmental committee in a report to the Home Secretary in 1936 recommended that Weil's disease be thenceforth scheduled as an industrial infection.⁵⁰

One of the first patients with Weil's disease seen in New York was a sewer worker,⁵¹ and 2 sewer workers in New York in whom the disease was recognized during 1938 and 1939 died of it.⁵² Two fish cutters in New York contracted the infection, and compensation was awarded both for a disease arising out of or in the course of employment.⁵³

44 Smith, J. Leptospiral Infections in Rats. Presence of Specific Leptospiral Immune Bodies in Serum and Their Relationship to Carrier Conditions, *J Hyg* **38** 521-526, 1938.

45 Fairley, N. H. Leptospirosis in the British Empire, *Acta Convent. tertii de trop. atque malar. morbis* **1** 387-395, 1938.

46 (a) Gulland, G. L., and Buchanan, G. Spirochaetosis Icterohaemorrhagica in East Lothian, *Brit. M. J.* **1** 313-314, 1924. (b) Buchanan, G. Spirochaetosis Icterohaemorrhagica, *ibid.* **2** 990-993, 1924. Spirochaetal Jaundice, Medical Research Council, Special Report Series, no. 113, London, His Majesty's Stationery Office, 1927.

47 Fairley, N. H. Weil's Disease Among Sewer Workers in London, *Brit. M. J.* **2** 10-14, 1934.

48 Stuart, R. D. Weil's Disease in Glasgow Sewer Workers, *Brit. M. J.* **1** 324-326, 1939.

49 (a) Morrissey, G. C. The Occurrence of Leptospirosis (Weil's Disease) in Australia, *M. J. Australia* **2** 496, 1934. (b) Drew, J. G. An Account of Weil's Disease in Queensland, *Brit. M. J.* **2** 1142-1143, 1934.

50 Home Office, Departmental Committee on Compensation for Industrial Diseases, Third Report to the Right Honourable The Secretary of State for the Home Department, London, His Majesty's Stationery Office, 1936.

51 Cushing, E. H. Leptospirosis Icterohaemorrhagica, *J. A. M. A.* **89** 1041-1043 (Sept. 24) 1927.

52 Farrell, E., Tiffany, E., and Rosenthal, M. Unpublished data.

53 Farrell, E. Weil's Disease. Compensable Infection in New York State, *New York State J. Med.* **39**:1969-1972, 1939.

Apart from occupational associations such as those just cited, Weil's disease has frequently occurred after accidental immersion,⁵⁴ though no instances of this sort have been recorded yet in the American scientific literature

Leptospirosis ictero-haemorrhagica is recognized far more often in Europe than in America. In Paris the disease is one *d'observation courante*,⁵⁵ and single cases of the classic type now attract too little attention to be reported in detail.⁵⁶ In Holland 374 cases were established between 1924 and 1938,^{34a} and there have been at least 248 adequately diagnosed cases of Weil's disease in Great Britain since 1922.^{34b} In the United States not all the proved cases have been reported, nor have all the reported cases been satisfactorily established by recovery and full identification of the causative organism or by satisfactory demonstration of specific immune properties in the blood serum. Recognition of the disease lags, although the work of Meyer⁵⁷ and others must eventually lead to a wider appreciation of the nature of this infection and to some reliable estimation of its extent.

The diagnosis of Weil's disease is a laboratory problem dependent for its solution on the alertness of the clinical staff, measured by the alacrity with which the clinical diagnosis is arrived at, on close ward-laboratory cooperation and on the experience of the bacteriologist in the isolation of the organism. Inoculation of guinea pigs with the blood in the first week or with the urine thereafter is the most valuable single diagnostic procedure, but serologic methods of diagnosis are also employed.

In the serologic diagnosis of Weil's disease some modification of the agglutination-lysis test may be used, but considerable experience is required for its reliable performance and interpretation.⁵⁸ The antibody titer may rise rapidly late in the third week of disease and reach a level of 1:40,000 or more by the end of the fifth week.⁵⁹ This level may be maintained for about three weeks, then it falls during a month or so to a much lower mark, at which it may remain for a number of years.

54 Schuffner, W. Recent Work on Leptospirosis, *Tr. Roy. Soc. Trop. Med. & Hyg.* **28** 7-37, 1934.

55 Troisier, J., Bariety, M., and Brouet, G. Spirochetose ictéro-hémorragique après morsure de rat. Méningite purulente, *Bull. et mem. Soc. med. d'hôp. de Paris* **50** 1451-1458, 1934.

56 Brumpt, E. Personal communication to the author.

57 Meyer, K. F., Stewart-Anderson, B., and Eddie, B. Epidemiology of Leptospirosis, *Am. J. Pub. Health* **29** 347-353, 1939.

58 Brown, H. C., and Broom, J. C. Observations on the Agglutination Test for Weil's Disease, *Brit. M. J.* **1** 1178-1179, 1939.

59 Kisker, A. Ueber den Verlauf des Agglutinationstiters bei Weilscher Krankheit, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **85** 383-391, 1935.

Macroscopic agglutination tests ⁶⁰ and complement fixation tests ⁶¹ have also been introduced. In performing serologic tests in cases in which leptospirosis is suspected, it is well to use both *L. icterohaemorrhagiae* and *L. canicola* as antigens. In certain cases testing with various strains of *L. icterohaemorrhagiae* may be necessary for exact identification of the immune bodies found in the patient's serum. Conservative interpretation of single reports should be a rigid rule.

Important practical points in the diagnosis of leptospirosis by inoculation of animals have recently been stressed by workers who urge the use of guinea pigs weighing less than 175 Gm ⁶² or even nursing animals ¹³. The animal first inoculated may show no leptospiras at autopsy but repeated subinoculations of material from successive animals may finally lead to the isolation of the organism. Cultivation of leptospiras has been successfully carried out on the chorioallantoic membrane of the chick embryo, ⁶³ but mediums such as Noguchi, Schuffner, Fletcher or Koithof have described serve the usual laboratory needs.

In the differential diagnosis of leptospirosis *icterohaemorrhagica* with jaundice, many other causes of icterus must be considered. Catarrhal jaundice, biliary obstruction, toxic hepatitis or acute yellow atrophy may be suggested in turn by successive stages of a leptospiral infection. Useful data in the early clinical recognition of Weil's disease are a history of occupational or accidental exposure to infection, signs of systemic invasion, fever, early prostration and myalgia, nephritis, anemia, leukocytosis and hemorrhages.

Small epidemics of leptospirosis *icterohaemorrhagica* may occur in similarly exposed groups with a common occupational background ⁶⁴ or with a commonly experienced immersion or other water accident.

60 Pot, A. W. A Macroscopic Agglutination Test in Weil's Disease, *Lancet* **1** 1290, 1936. Smith, J., and Tulloch, W. J. A Macroscopic Agglutination Test for Diagnosis of Weil's Disease, *ibid* **2** 846-850, 1937. Brown, H. C. A Rapid Presumptive Serological Test for Weil's Disease, *Brit. M. J.* **2** 1183, 1939.

61 Pot, A. W., and Dornick, C. G. J. The Complement Fixation Test in the Diagnosis of Weil's Disease, *J. Path. & Bact.* **43**:367-372, 1936. Gaetgens, W. Ueber die praktische Bedeutung der serologischen Untersuchung, insbesondere der Komplementbindungsreaktion, für die Diagnose der Weilschen Krankheit, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **96**:287-319, 1939.

62 Syverton, J. T., Berry, G. P., and Stiles, W. W. The Diagnosis of Weil's Disease (Infectious Jaundice), *J. Clin. Investigation* **17**:522, 1938.

63 Morrow, G., Syverton, J. T., Stiles, W. W., and Berry, G. P. The Growth of *Leptospira Icterohemorrhagiae* on the Chorio-Allantoic Membrane of the Chick Embryo, *Science* **88** 384-385, 1938.

64 Davidson and Smith ^{34b}. Gulland and Buchanan ^{16a}. Buchanan ^{46b}. Morrissey ^{49a}. Drew ^{49b}.

Institutional epidemics of jaundice have been attributed to Weil's disease⁶⁵ and indexed as spirochetel jaundice,⁶⁶ but the evidence for a viral cause of infective hepatitis (epidemic catarrhal jaundice)⁶⁷ is too convincing to be shaken by anything short of the isolation of *L. icterohaemorrhagiae* directly from patients or the demonstration of specific antibodies in changing titer in the blood serum of a significant proportion of those affected. Careful studies in the past⁶⁸ have failed to demonstrate an etiologic relationship between *L. icterohaemorrhagiae* and epidemic infectious jaundice. Harmless leptospires of typical form occur in nature, so the finding of leptospires of unidentified species in local collections of water during the course of an outbreak of jaundice⁶⁹ cannot be regarded as significant.

The genesis of icterus in leptospirosis icterohaemorrhagica is obscure. Kaneko once concluded that the jaundice resulted from intra-acinous biliary obstruction without actual blockage of the bile channels, but he has modified this opinion,⁷⁰ following the work of Oka,⁷¹ who decided that cellular dissociation resulted in dilatation and rupture of the bile capillaries, with escape of bile into the general circulation. In Oka's human cases the blood serum gave a direct van den Bergh reaction. In cases of the infection in guinea pigs the reaction is apparently indirect,⁷² and the jaundice is attributed to extensive destruction of blood with retention of bilirubin resulting from functional impairment of the liver due to edema of the organ.

Weil's disease and yellow fever are both characterized by hepatitis, but yellow fever causes specific histologic changes in the liver which can be differentiated from those found in leptospirosis icterohaemori-

65 Slesinger, H. A., and Zeligman, I. Acute Infectious Duodenitis (Infectious Jaundice). Report of Seventy-Six Cases, *J. Pediat.* **14** 213-219, 1939.

66 Quarterly Cumulative Index Medicus **25** 724, 1939.

67 Findlay, G. M., MacCallum, F. O., and Murgatroyd, F. Observations Bearing on the Aetiology of Infective Hepatitis (So-Called Epidemic Catarrhal Jaundice), *Tr. Roy. Soc. Trop. Med. & Hyg.* **32** 575-586, 1939.

68 Wadsworth, A., Langworthy, H. V., Stewart, F. C., and Moore, A. Infectious Jaundice Occurring in New York State, *J. A. M. A.* **78** 1120-1121 (April 15) 1922. Langworthy, V., and Moore, A. C. A Study of *Leptospira Icterohaemorrhagiae*, *J. Infect. Dis.* **41** 70-91, 1927.

69 Willett, J. C., Sigoloff, E., and Pfau, C. L. An Institutional Outbreak of Epidemic Jaundice, *J. A. M. A.* **106** 1644-1646 (May 9) 1936.

70 Kaneko, R. Ueber den Ikterus bei Spirochaetosis ikterohaemorrhagica Inada (Weil'sche Krankheit), *Schweiz. med. Wchnschr.* **65** 531-532, 1935.

71 Oka, T. Ueber den Ikterus bei Spirochaetosis icterohaemorrhagica Inada (Weilsche Krankheit), *Klin. Wchnschr.* **14** 785-786, 1935.

72 Busch, H. Ueber die Ursache des Ikterus bei der experimentellen Weilschen Krankheit, *Beitr. z. path. Anat. u. z. allg. Path.* **96** 233-247, 1936.

rhagica⁷³ In yellow fever the liver shows hyaline areas of Councilman necrosis, extensive fatty degeneration and cellular dissociation of such an extreme degree that all lobular structure is lost Councilman necrosis, is never seen in Weil's disease nor is there as much fatty infiltration or such extensive separation of the liver cells⁷⁴ The anatomic differentiation of yellow fever and Weil's disease is particularly important in those parts of the world where the diseases coexist and where through a viscerotome service⁷⁵ search is continually being made for silent foci of yellow fever

The early administration of 30 to 60 cc of immune serum with an antileptospiral titer of 1:20,000 or more⁷⁶ is of prime importance in the treatment of Weil's disease No commercial antiserum is generally available in the United States but in Europe such serums are widely used

Prophylactic immunization against Weil's disease has been tried on a large scale in Japan, with apparently favorable results, but vaccination of human subjects in Scotland with 1 to 2 cc of killed culture caused only small amounts of lytic antibody to appear in the blood stream⁷⁷

VITAMIN K AND BLOOD COAGULATION

The earlier literature dealing with the relationship between prothrombin deficiency and the bleeding tendency of jaundiced patients and the importance of vitamin K in correcting this disturbance was reported in the review for 1938⁷⁸ Since then, the literature dealing with various phases of this problem has increased voluminously It has been summarized in detail by Quick⁷⁹ and so need not be reviewed

73 Snijders, E. P. Zur pathologischen Anatomie der Leber bei Gelbfieber und Weilscher Krankheit, in *Arbeiten über Tropenkrankheiten und deren Grenzgebiete* (Bernard Nocht's Festschrift), Hamburg, Friederichsen, 1937, p. 539

74 Bablet, J. Sur le diagnostic différentiel entre la spirochetose ictero-hémorragique et la fièvre jaune par l'examen histologique du foie, *Bull. Office internat. d'hyg. pub.* **28**: 2346-2353, 1936

75 Rickard, E. R. The Organization of the Viscerotome Service of the Brazilian Cooperative Yellow Fever Service, *Am. J. Trop. Med.* **17**: 163-190, 1937

76 Zimmermann, E., and Arjona, E. Serologischer Titer und Heilwert der Seren gegen Weilsche Krankheit, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **84**: 111-117, 1935

77 Smith, J. Vaccination of Guinea Pigs and Human Beings Against Leptospiral Infections, *J. Hyg.* **37**: 261-270, 1937

78 Greene, C. H., and Hotz, R. Liver and Biliary Tract. A Review for 1938, *Arch. Int. Med.* **63**: 778-808 (April) 1939

79 Quick, A. J. A Classification of Hemorrhagic Diseases Due to Defects in the Coagulation Mechanism of the Blood, Based on Recently Published Studies, *Am. J. M. Sc.* **199**: 118-132, 1940

further at this time. The most important development during the year has been the isolation of vitamin K in crystalline form, the determination of its chemical structure and its chemical synthesis. This goal was reached practically simultaneously by several different groups of investigators,⁸⁰ and accounts of this dramatic race have been reported by Fieser⁸¹ and by Doisy and his associates.⁸²

These studies established that vitamin K, prepared from alfalfa, is 2-methyl-3-phytyl-1,4-naphthoquinone. An extensive study of the activity of related naphthoquinones showed that 2-methyl-1,4-naphthoquinone was the most active of these and was at least as efficient as the naturally occurring vitamin K. Since it is slightly water soluble, it can be given intravenously. When given by mouth, it may be absorbed more readily than the natural vitamin K. The clinical uses of 2-methyl-1,4-naphthoquinone in the treatment of prothrombin deficiency have been reported by a series of investigators.⁸³ Doses of from 0.6 to 10 mg daily have sufficed to control the hemorrhagic phenomenon and restore the blood prothrombin to normal. No toxic effects have been reported and while further study is required, the introduction of the use of this compound into clinical practice apparently represents a real therapeutic triumph.

DIET IN RELATION TO HEPATIC INJURY

The current widespread use of carbohydrate diets in the treatment of jaundice and hepatic disease is based on two scientific premises:

1. The intermediary metabolism and oxidation of carbohydrate make less demands on the liver than the oxidation of either protein or

80 Binkley, S. B., Cheney, L. C., Holcomb, W. F., McKee, R. W., Thayer, S. A., MacCorquodale, D. W., and Doisy, E. A. The Constitution and Synthesis of Vitamin K₁, *J. Am. Chem. Soc.* **61** 2558-2559, 1939. Fieser, L. F., Campbell, W. B., Fry, E. M., and Gates, M. D. Synthetic Approach to Vitamin K₁, *ibid.* **61** 2559, 1939. Almquist, H. J., and Klose, A. A. Synthetic and Natural Anti-Hemorrhagic Compounds, *ibid.* **61** 2557-2558, 1939.

81 Fieser, L. F. The Synthesis of Vitamin K₁, *Science* **91** 31-36, 1940.

82 Doisy, E. A., Binkley, S. B., Thayer, S. A., and McKee, R. W. Vitamin K, *Science* **91** 58-62, 1940.

83 Frank, H. A., Hurwitz, A., and Seligman, A. M. The Treatment of Hypoprothrombinemia with Synthetic Vitamin K₁, *New England J. Med.* **221** 975, 1939. Macfie, J. M., Bacharach, A. L., and Chance, M. R. A. Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice, *Brit. M. J.* **2** 1220-1223, 1939. Butt, H. R., Snell, A. M., Osterberg, A. E., and Bollman, J. L. Treatment of Hypoprothrombinemia. Use of Various Synthetic Compounds Exhibiting Antihemorrhagic Activity (Vitamin K₁ Activity), *Proc. Staff Meet., Mayo Clin.* **15** 69-73, 1940. Rhoads, J. E., and Fliegelman, M. I. Use of 2-Methyl-1,4-Naphthoquinone (A Synthetic Vitamin K Substitute) in the Treatment of Prothrombin Deficiency, *J. A. M. A.* **114** 400-401 (Feb. 3) 1940. Sharp, E. A. Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone, *ibid.* **114** 439-440 (Feb. 3) 1940. Broun, G. O., in discussion on Sharp.

fat The feeding of enough carbohydrate to provide for the caloric requirements of the patient and keep the intermediary metabolism on a carbohydrate basis is therefore one way of putting the liver in a state of physiologic rest

2 Laboratory animals on diets high in carbohydrate whose livers contain adequate reserves of glycogen are more resistant to the effects of hepatic toxins, such as chloroform⁸⁴

The older literature was reviewed by Davis and Whipple⁸⁵ and need not be considered in detail at the present time

The experimental study of the effects of diet on the susceptibility of the liver to injury by chloroform has recently been reinvestigated by Goldschmidt, Vars and Ravdin⁸⁶ and by Miller and Whipple⁸⁷ Messinger and Hawkins⁸⁸ have studied the effect of diet on the susceptibility of the liver to injury by arsphenamine All are in agreement that fat is injurious, for the susceptibility of the liver to injury increases progressively with an increase in lipids in the liver Their different experiments were also in agreement in indicating that a diet high in protein markedly reduced the susceptibility of the liver to injury by either chloroform or arsphenamine Protein depletion by diet or plasmapheresis increased the susceptibility to chloroform as the bodily stores of protein were depleted Diets high in carbohydrate proved to be beneficial but not quite as effective as those high in protein Whether the benefit obtained from carbohydrate diets in these experiments was due to a direct effect of the carbohydrate on the liver or to an indirect influence by virtue of an action on protein or to the fact that carbohydrate diets usually reduce the lipid content of the liver is still unsettled

These experiments are interesting because of the increasing mass of evidence pointing to disturbances in protein metabolism in hepatic

84 Opie, E L, and Alford, L B The Influence of Diet on Hepatic Necrosis and the Toxicity of Chloroform, *J A M A* **62** 895-896 (March 21) 1914, Diet and the Hepatic Lesions of Chloroform, Phosphorus or Alcohol, *J Exper Med* **21** 1-20, 1915

85 Davis, N C, and Whipple, G H The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, *Arch Int Med* **23** 612-635 (May) 1919

86 Goldschmidt, S, Vars, H M, and Ravdin, I S The Influence of the Foodstuffs upon the Susceptibility of the Liver to Injury by Chloroform and the Probable Mechanism of Their Action, *J Clin Investigation* **18** 277-289, 1939

87 Miller, L L, and Whipple, G H Chloroform Liver Injury Increases as Protein Stores Decrease Studies in Nitrogen Metabolism in These Dogs, *Am J M Sc* **199** 204-216, 1940

88 Messinger, W J, and Hawkins, W B Arsphenamine Liver Injury Modified by Diet Protein and Carbohydrate Protective, but Fat Injurious, *Am J M Sc* **199** 216-225, 1940

disease Changes in the serum protein and hypoproteinemia, apart from prothrombin deficiency, accompany serious diseases of the liver Such evidence would seem to indicate the desirability of feeding protein-rich diets to patients with hepatic disease

This evidence, however, should not be accepted without reservations Hahn, Massen, Nencki and Pavlov⁸⁹ and Fischler⁹⁰ long ago pointed out the susceptibility of the dog with a damaged liver (Eck fistula) to the feeding of excessive amounts of meat—the so-called “Fleisch intoxication” Mann and Bollman⁹¹ have confirmed these observations They later found that the feeding of meat extract produced the same effects as meat It is also noteworthy that Goldschmidt, Vais and Ravdin⁹² used casein for their high protein diets More work designed to compare the effects of meat as contrasted to protein diets is desirable Until such studies are reported, the clinician wishing to follow the lead of these investigators will increase the protein content of the diet for patients with hepatic disease but will still avoid excessive amounts of protein and choose dairy proteins in preference to meat

CIRRHOSIS VERSUS FIBROSIS OF THE LIVER

The proper nomenclature of the various types of hepatic diseases is by no means settled, and only too frequently the same term is used to indicate quite different conditions Gibson and Robertson⁹² call attention to the confusion in the use of the term “cirrhosis” They quote numerous authorities and point out that even among pathologists a definition of hepatic cirrhosis acceptable to all is difficult to find There is general agreement that parenchymal destruction and scarring must be present There is less agreement on the importance of parenchymal repair When only parenchymal destruction and scarring are required by the definition of hepatic cirrhosis, it is difficult to exclude numerous conditions not commonly included within this group, for many agents will produce parenchymal destruction and scarring Gibson and Robertson therefore limit the definition of hepatic cirrhosis to conditions in which there is evidence of parenchymal degeneration and fibrous and nodular parenchymal repair

89 Hahn, M, Massen, V, Nencki, M, and Pavlov, J Die Ecksche Fistel zwischen unterer Hohlvene und Pfortader, Arch f exper Path u Pharmakol **32** 161, 1893

90 Fischler, F Physiologie und Pathologie der Leber nach ihrem heutigen Stande, ed 2, Berlin, Julius Springer, 1925

91 Bollman, J L, and Mann, F C The Physiology of the Impaired Liver, Ergebn d Physiol **38** 445-492, 1936

92 Gibson, W R, and Robertson, H E So-Called Biliary Cirrhosis, Arch Path **28** 37-48 (July) 1939

Using this criterion of cirrhosis, they studied a series of cases of so-called biliary cirrhosis following obstructive jaundice. Both their review of the literature and their study of cases indicated that in cases of this type there are parenchymal degenerative changes of various sorts, an increase in the portal connective tissue, an apparent increase in the interlobular ducts, bile thrombi and collections of cells, such as polymorphonuclear leukocytes, in the portal connective tissue. Emphasis is placed on bile stasis, fibrosis of some degree and parenchymal degeneration. The outstanding feature is the parenchymal degeneration. Gibson and Robertson also point out that the results of parenchymal degeneration frequently dominate the clinical picture, so that the prognosis should be guarded unless the biliary obstruction can be relieved and hepatic recovery permitted. They therefore insist that this condition would be more suitably described as *hepatic atrophy*. This would place the emphasis on the parenchymal degeneration associated with biliary obstruction and jaundice.

Gibson and Robertson further report that in not quite 10 per cent of their cases of biliary obstruction true hepatic cirrhosis was present. These cases were characterized by a history of intermittent or fluctuating jaundice. It seems possible, therefore, that in these cases intermittent episodes of obstruction with associated parenchymal destruction alternating with periods of relief from jaundice and consequent opportunity for parenchymal repair may have led to the production of true *hepatic cirrhosis from biliary obstruction*.

It was therefore suggested by Gibson and Robertson that the term "biliary cirrhosis" be dropped. Cases in which hepatic parenchymal damage without signs of regeneration follows obstruction of the bile ducts should be classified as instances of *hepatic atrophy*. Cases of the infrequent combination of biliary obstruction, obstructive jaundice and true hepatic cirrhosis should be classified as *cirrhosis from biliary obstruction*.

The same difficulties of nomenclature arise in connection with the changes in the liver produced by chronic passive congestion, the so-called cardiac cirrhosis. This problem has been reported in detail by Boland and Willis⁹³ and by Katzin, Waller and Blumgart⁹⁴.

They agree that the most frequent pathologic picture seen in the liver as a result of prolonged or repeated episodes of congestive heart failure is degeneration of the central portion of the lobules with or with-

⁹³ Boland, E. W., and Willis, F. A. Changes in the Liver Produced by Chronic Passive Congestion, with Special Reference to the Problem of Cardiac Cirrhosis, *Arch Int Med* **62** 723-739 (Nov.) 1938.

⁹⁴ Katzin, H. M., Waller, J. V. and Blumgart, H. L. "Cardiac Cirrhosis" of the Liver. A Clinical and Pathologic Study, *Arch Int Med* **64** 457-470 (Sept.) 1939.

out condensation of the reticulum. It is generally assumed that central lobular atrophy results from chronic passive congestion of gradual onset and that necrosis develops when cardiac failure occurs more abruptly or is of greater severity. Boland and Willius⁹³ found that they could not predict from the clinical history and physical findings whether the liver would show atrophy or necrosis. The possibility of an additional toxic factor in their cases could not be excluded.

In the more severe cases, especially those with a history of multiple episodes of heart failure, there was considerable evidence of condensation and thickening of reticulum, especially in the areas of degeneration. This thickening of the reticulum on occasion went on to true fibrosis. Both authors insist that condensation of reticulum does not warrant the use of the term "cardiac cirrhosis" but accept it as signifying morphologic increase in connective tissue in the liver consequent to congestive failure but point out that clinical cardiac cirrhosis signifies the extreme fibrosis which results from chronic passive congestion and causes evidences of portal obstruction.

If the definition of cirrhosis propounded by Gibson and Robertson, i. e., hepatic degeneration, fibrosis and parenchymal regeneration, be accepted, and we believe it should be, then these cases of Boland and Willius and of Katzin, Waller and Blumgart should be referred to as examples of cardiac fibrosis of the liver and not of cardiac cirrhosis.

Boland and Willius also include in their report a few cases in which in addition to the degenerative changes of chronic passive congestion and fibrous tissue proliferation there were areas of adenomatous regeneration of the few hepatic cells remaining in the collapsed lobules.

There was a history of multiple episodes of cardiac failure, and Boland and Willius suggest that during the intervals of partial cardiac recovery there was fibrosis of the areas of complete lobular destruction while the partially destroyed lobules underwent regenerative changes. These few cases apparently represent cases of true cirrhosis, but even in them the possibility of contributing toxins could not be excluded. Cardiac cirrhosis in the strictest sense must be accepted as a possible clinical and pathologic entity, but these studies emphasize its rarity.

GENERAL TEXTBOOKS

Attention is invited to two monographs recently published which deal with diseases of the gallbladder and biliary tract (Carter, Greene and Twiss⁹⁵, Walters and Snell⁹⁶). Each is primarily a report of the

95 Carter, R. F., Greene, C. H., and Twiss, J. R. *Diagnosis and Management of Diseases of the Biliary Tract*, Philadelphia, Lea & Febiger, 1939.

96 Walters, W., and Snell, A. M. *Disease of the Gallbladder and Bile Ducts*, Philadelphia, W. B. Saunders Company, 1940.

experience of its writers. Each presents a statistical study of an extensive surgical experience.

The most noteworthy feature of the two textbooks, however, is the difference in the point of view. The volume of Walters and Snell follows the traditional form and stresses the anatomic and pathologic changes in the gallbladder and biliary tract. Cholecystitis and gallstones are accepted as unfortunate but real conditions. The treatment is surgical, and the operation is reported as curative.

The volume of Carter, Greene and Twiss departs from the traditional in that the point of view is primarily physiologic, and the emphasis is on function rather than on form. They agree that gallstones and a functionless, infected, fibrotic gallbladder represent pathologic entities which necessitate surgical methods of treatment but emphasize that such conditions in many cases apparently arise as the result of a preceding functional disturbance. If the physician can recognize and by appropriate medical therapy correct this functional disturbance, the development of the surgical lesion may be prevented. Furthermore, surgical operation does not always correct the functional disturbance, and the patient requires careful postoperative as well as preoperative medical management. The textbook therefore stresses the selection of diet and the details of medical management. The diagnostic value of duodenal drainage likewise is stressed.

These differences in point of view are determined by the interests of the authors and the different types of clinical material seen by each group. Primarily, the differences are matters of organization and method of presentation. The careful reader will find that in the majority of instances the question of the choice of medical or of surgical methods of treatment and the methods of treatment considered appropriate are the same.

News and Comment

Second Graduate Course in Internal Medicine, Vanderbilt University Medical School—This course consists of supervised work with patients in the medical outpatient service, including the related specialties, experience in the diagnostic laboratories, assigned reading, seminars and conferences, including pathologic and radiologic conferences and autopsy study, and directed study and seminars in the preclinical sciences, particularly physiology and biochemistry. Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis will be required. The course extends over a period of one year and is open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school. The second course begins July 1, 1940. The tuition fee is \$300.

Applications for admission and fellowships will be received by the Director of Postgraduate Instruction, Vanderbilt University Medical School, until April 15, 1940.

Three fellowships are available for this course. These fellowships, which provide tuition, board and lodging, are open to those who meet the requirements mentioned and will be awarded on the basis of training and recommendations.

American Heart Association—The sixteenth scientific sessions of the American Heart Association, Inc., will be held at the Roosevelt Hotel, New York, June 7 and 8. On the first day there will be a program on the heart, and on the second day the program of the Section for the Study of the Peripheral Circulation will be presented.

American Public Health Association—The sixty-ninth annual meeting of the American Public Health Association will be held in Detroit, October 8 to 11. The Book-Cadillac Hotel will be the headquarters. Dr. Reginald M. Atwater, 50 West Fiftieth Street, New York, is executive secretary.

The Michigan Public Health Association, the American School Health Association, the International Society of Medical Health Officers, the Association of Women in Public Health and a number of other allied and related organizations will meet in conjunction with the association.

The Michigan Committee on Arrangements is headed by Mr. Abner Larned, of Detroit. Dr. Henry F. Vaughan, health commissioner of Detroit, is executive secretary of the committee.

American Association for the Advancement of Oral Diagnosis—The annual meeting of the American Association for the Advancement of Oral Diagnosis will be held on Oct. 17 and 18, 1940, at the building of the New York Academy of Medicine, 2 East One Hundred and Third Street, New York.

Further information and membership blanks may be procured from Dr. H. Justin Ross, executive office, 515 Madison Avenue, New York.

Industrial Health—The twenty-fifth annual meeting of the American Association of Industrial Physicians and Surgeons, together with the first annual meeting of the American Industrial Hygiene Association, will be held at Hotel Pennsylvania, New York, June 4 to 7, 1940. Technical and scientific exhibits will be a feature of the convention. The dinner on Thursday evening, June 6, will be the occasion of the presentation of the William S. Knudsen award for the year of 1939-1940.

Book Reviews

Fisiopatologia dello scompenso cronico di circolo By D Cesa-Bianchi and M Calabresi Pp 187 Rome Luigi Pozzi, 1936

This work digests thoroughly the majority of the recent European and American articles on the pathogenesis of cardiac and circulatory decompensation. The results of studies carried out in the authors' clinic are presented in essence, but no quantitative data are offered. Most of their work has been concerned with the biochemical features of circulatory failure. Much significance is attached by them to the defects of lactic acid metabolism, the oxygen debt and the increased basal metabolic rate of decompensated patients. The authors revel in the paradoxes which are apparent on comparing the theories and facts relating to decompensation. They argue that the majority of the data are complementary, not contradictory. They think that decompensation of the circulation occurs when the cardiac output is inadequate for the tissue needs. The decreased blood supply causes capillary stasis, tissue hypoxia and the formation of acid metabolites. Concurrently with the diminution in output, there must be a damming back of that blood which would normally be ejected. This causes retrograde stasis and venous hypertension and further insults the tissues injured by the hypoxia. This synthesis, then, is a fusion of the theories of forward and backward failure.

Notable omissions from lengthy consideration are the theories of dyspnea that Peabody, Harrison and others have advanced.

Although the paper was prepared for a clinical congress, the clinical implications of the data are meagerly presented, and no therapeutic deductions are made.

Diseases of the Skin By Richard L. Sutton and Richard L. Sutton Jr. Tenth edition. Price, \$15.00. Pp 1549, with 1452 illustrations and 21 color plates. St. Louis. The C. V. Mosby Company, 1939.

In this tenth edition the authors have attempted, very successfully, to correlate descriptions and concepts of disorders of the skin with general medicine and biology—to answer the question "What is going on?" rather than to content themselves with classification. This approach has necessitated radical rearrangement and the inclusion of much material not to be found in the ninth edition. Also added are ten color plates and a large number of new illustrations. The bibliography is extensive and includes many additional comments intended primarily for the special student. The book should serve as a valuable work of reference for the internist.

A Textbook of Medicine By American Authors. Edited by Russell L. Cecil. Fourth edition. Price, \$9. Pp 1,614, with 42 illustrations. Philadelphia. W. B. Saunders Company, 1937.

Cecil's "Textbook of Medicine" has established itself so solidly that the periodic appearance of new editions is taken as a matter of course. In this fourth edition the general scheme and format are preserved, and, as far as the reviewer can see, the various articles have been brought well up to date. The book is to be recommended especially as a miniature system of medicine, most of the articles being written by recognized authorities, but the large number of contributors makes one feel the lack of a uniform point of view. For purposes of general reference there is no better book.

Results Followed Up for Twenty Years After Grafting of the Thyroid in Cases of Myxedematous Creatinism By Serge Voronoff Translated by Theodore C Merrill Bulletin 492, Société de pathologie comparative, Paris, October 1937

Case reports are presented of 3 myxedematous cietins each of whom received a thyroid transplant either from his mother or from an ape. The submitted photographs, the data on physical and mental growth and the basal metabolism indicate that the transplanted glands truly "took." The author believes that, aside from the usual precautions taken with glandular transplants, the grafting of the gland to its usual site is important.

Clinical Allergy By Louis Tuft, M.D. Price, \$8 Pp 711, with 82 illustrations Philadelphia W B Saunders Company, 1937

As a number of excellent texts on allergy have appeared in the past few years, one wonders on seeing still another whether it has any novel features. The reviewer is very favorably impressed with Tuft's compact treatise, which is well written and seems to cover the subject in a thorough and yet not extreme manner. Of particular value to the reader and the student are the various excellent illustrations, the summary of much material in tabular form and the charts and diagrams, such as those of the distributions of various pollens.

PANCREATIC LITHIASIS ASSOCIATED WITH PANCREATIC INSUFFICIENCY AND DIABETES MELLITUS

REPORT OF TWO CASES

SAMUEL S ROCKWERN, M D *

CINCINNATI

AND

DANIEL SNIVELY, M D

ROCK ISLAND, ILL

Pancreatic lithiasis is a relatively rare pathologic entity. A careful study of the literature published before 1939 reveals a total of approximately 125 reported cases of the disease. According to Witherspoon,¹ until 1935 operation had been performed in only 28 cases and in but 4 of these had a diagnosis been made prior to operation.

It was our privilege to observe 2 patients with this disease who were admitted to the medical service of the Cincinnati General Hospital within the period of one month. The condition of the first patient was diagnosed during life and that of the second at autopsy. In the first case we were able to confirm the diagnosis by demonstrating a definite lack of pancreatic enzymes both in the duodenal fluid and in the feces. In addition to the usual management of a diabetic patient, we administered rather large amounts of a potent preparation of pancreatic enzymes and observed the favorable effect.

REPORT OF CASES

CASE 1—The diagnosis was made during the life of the patient by roentgen examination and by the typical signs and symptoms of pancreatic lithiasis. The patient, Mrs. L. F., a 50 year old white woman, had spent most of her life in Tennessee. She was in good health until four years prior to her admission to the hospital. At that time she began to have typical signs and symptoms of diabetes mellitus. A physician informed her that she had diabetes, placed her on a special

* Fellow in Diabetes, the University of Cincinnati College of Medicine.

From the College of Medicine, Department of Internal Medicine of the University of Cincinnati and the Cincinnati General Hospital. This investigation was aided by the Espy Fund for the Study of Diabetes.

1 Witherspoon, J. Pancreatic Lithiasis, *South M J* 11 1064, 1937.

diet and instructed her to take insulin. She did not adhere to the diet, nor did she take insulin. Shortly after this time she had an attack of severe, knifelike pain in the right upper quadrant of the abdomen, which radiated to the epigastrium and posteriorly to the right scapular region. At the same time she became nauseated, and her abdomen became distended with gas. Diarrhea occurred, with the passage of six to eight light yellow, soft, fatty stools, which contained undigested particles of food. The attack then subsided spontaneously, and the patient had no repetition of the episode for about six months, when a similar attack occurred. The attacks then became more frequent and of greater severity and duration. During the year preceding admission to the hospital attacks occurred on an average of

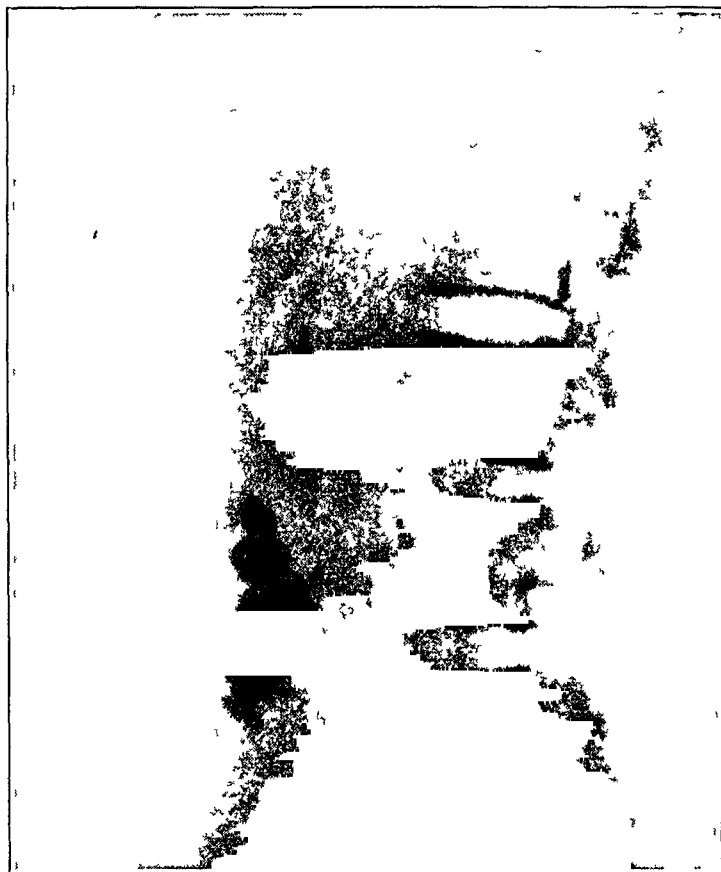


Fig 1—Lateral roentgenographic view of the abdomen in case 1, illustrating infiltration of calculi into the head, body and tail of the pancreas

every two or three months. In the two weeks before admission she had four rather severe attacks. The attacks characteristically occurred about two hours after eating, the pain lasting for about three hours. The pain was not relieved by ingestion of food. The signs and symptoms of diabetes had persisted from the time of onset until the date of admission to the hospital. At the age of 9 years the patient suffered from malaria. When she was 32 she was operated on for "female trouble." The past history was otherwise of no significance.

Physical examination revealed emaciation and evidence of wasting. The temperature was 98.6 F, the pulse rate 84, the respiratory rate 20 and the blood pressure 110 systolic and 60 diastolic. She weighed 90 pounds (40.8 Kg). The skin was dry, loose, inelastic and wrinkled. It had a yellowish brown color similar to that often associated with malignancy. The right kidney was palpable,

there were tenderness and muscle spasm in the right upper quadrant of the abdomen, but no mass could be felt there or in the epigastrium. A ventral hernia was present below the umbilicus, in the region of the scar from a pelvic operation. Physical examination gave otherwise essentially negative results.

Laboratory examination revealed a negative Kahn reaction of the blood and a red cell count of 4,450,000, with a hemoglobin value of 13.4 Gm. The white cell count and the differential count were within normal limits. Examination of the urine revealed a trace of albumin, a 3 plus reaction for sugar and a 1 plus reaction for acetone. The stool was voluminous, light tan, soft and oily, with many particles of grossly undigested meat and vegetables. Microscopic examination revealed many striated muscle fibers, vegetable fibers and fat globules. The blood sugar during fasting was 344 mg per hundred cubic centimeters. A dextrose

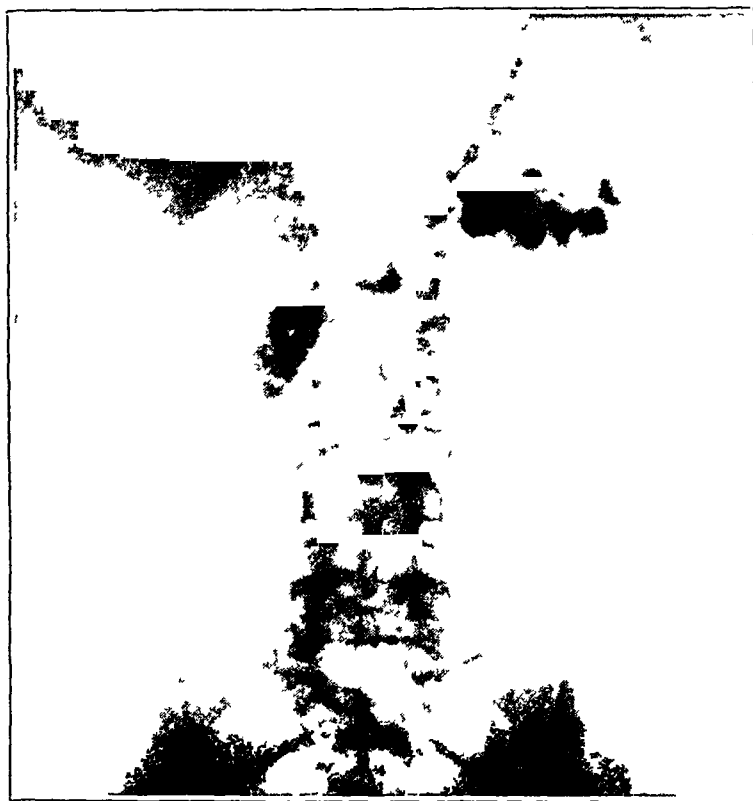


Fig 2—Anteroposterior roentgenographic view of the abdomen in case 1, showing calculi in the head, body and tail of the pancreas

tolerance test was performed, 100 Gm of dextrose being administered by mouth. One-half hour later the value for blood sugar was 400 mg per hundred cubic centimeters, one hour later it was 488 mg, two hours later, 500 mg, and three hours later, 513 mg. The cholesterol content of the blood was 125 mg, the icteric index, 8, the value for blood phosphatase, 5.3 mg, and the blood phosphorus content, 2.8.

Analysis of the gastric contents revealed the presence of considerable mucus, a trace of bile and the absence of free acid in the fasting specimen, with the presence of 15 degrees of free acid, fifteen minutes after the intramuscular administration of histamine. The corresponding amounts of total acid were 3 degrees for the fasting specimen and 4 degrees for the fifteen minute specimen. Microscopic examination of the gastric contents revealed a few white and red cells and many particles of undigested food.

Repeated drainage of the gallbladder revealed A, B and C bile in normal quantities. No bile-stained cells were present, and cholesterol crystals were not detected. A large number of fat globules were present in all three types of bile.

Tests to detect quantitatively the deficiency of the pancreatic enzymes were performed on specimens of the duodenal juice, feces and urine. Tryptic activity of the duodenal juice as determined by the Gross method was under 1 unit, the average normal value being 25 units. The amylopsin content of the duodenal juice as determined by the Myers and Fine method was 25 units, the average normal amylolytic activity of duodenal juice being 40 units. Tryptic activity of a specimen of stool as determined by the Gross method was 8,000 units, as compared with an average normal value of 12,500 units. The amylase content of the stool as determined by the Myers and Fine method was 10,000 units, the normal value ranging from 30,000 to 60,000 units². The amylase content of the urine was normal.

A series of roentgenograms of the gastrointestinal tract revealed diffuse areas of calcification in the region of the pancreas (figs 1 and 2). No pancreatic calcifications could be demonstrated by fluoroscopic examination. Roentgenograms of the gallbladder did not give visualization of this organ.

The patient was placed on a diet for diabetic patients, high in carbohydrates and low in fats, and was given protamine zinc insulin in conjunction with a commercial preparation of pancreatic enzymes. The attacks of pain became much less frequent and relatively mild, the diarrhea disappeared, and the patient gained 10 pounds (4.5 Kg). A short time after her discharge the blood sugar during fasting was 90 mg per hundred cubic centimeters, and the urine was free of sugar and acetone.

CASE 2—Mrs F. B., a 38 year old Negress, was admitted to the hospital in coma at 4:30 p. m. on March 13, 1938. The history, as obtained later from her husband, revealed that the patient had been receiving treatment for diabetes mellitus for several years at her home in Georgia. She had been taking insulin regularly. About three months before admission to this hospital she was in a hospital in Georgia for several weeks. At that time she was said to have been unconscious for five days. The patient came to Cincinnati ten days before being admitted to this hospital. She had made no provision for receiving insulin during her stay, and the day after her arrival she complained of sore throat and malaise. She went to bed and became delirious. Five days before she was brought to the hospital she lapsed into unconsciousness.

Physical examination on admission revealed emaciation. The eyeballs were soft and sunken. The heart rate was rapid, and the sounds were faint. Rales were heard at the bases of both lungs, but these were not marked. The abdomen was tense, no masses could be palpated. The patellar reflex was absent on both sides.

The red cell count and the value for hemoglobin were within normal limits. The white cell count was 12,800, with 94 per cent neutrophils, 5 per cent lymphocytes and 1 per cent monocytes. Urinalysis revealed albumin, 1 plus, acetone, 2 plus, and sugar, 4 plus, with a few white blood cells and occasional epithelial cells and hyaline and granular casts. The sedimentation rate was 24 mm in one hour. The sugar content of the blood was 417 mg per hundred cubic centimeters, the carbon dioxide-combining power was 17 volumes per cent, and the value for urea nitrogen was 55 mg per hundred cubic centimeters.

² Levinson, S. A., and MacFate, R. P. *Clinical Laboratory Diagnosis*, Philadelphia, Lea & Febiger, 1937.

On admission the patient received insulin, intravenous injections of fluids, lavage with a solution of sodium bicarbonate and application of heat to the body. However, she became progressively worse. The blood pressure fell from its highest reading of 72 systolic and 48 diastolic to a pressure which was too low to register. The blood sugar content shortly before death was 440 mg per hundred cubic centimeters, with a carbon dioxide-combining power of 25 volumes per cent. The patient died five hours after admission.

The interesting postmortem observations as reported by Dr R Ritterhoff, of the department of pathology of this hospital, were in the pancreas. This organ was

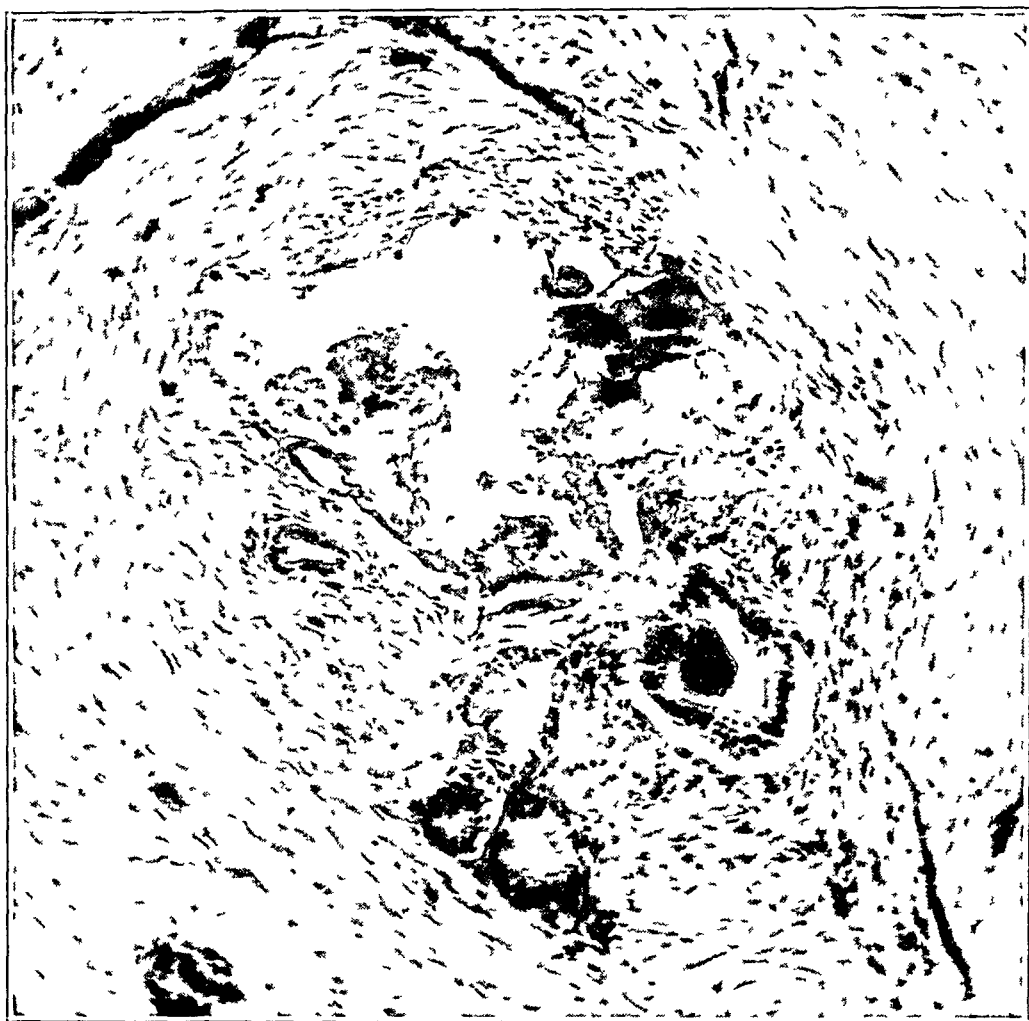


Fig 3—Microscopic section of the pancreas in case 2, illustrating extreme fibrosis with chronic interstitial inflammation, marked arteriosclerosis and arteriolosclerosis and dilated pancreatic ducts in which calcium is present. Note the pinching off of the acini and islets of Langerhans.

small and atrophic and was pink-white. It weighed 50 Gm. The tail and body appeared as a thin band, measuring 1.4 cm in the greatest width. On palpation the pancreas was stony hard and very nodular. Cut sections of the nodular areas revealed a thin envelop of pancreatic tissue surrounding soft white calcareous masses, which varied from 1 to 3 cm in diameter. The pancreatic ducts were thickened, dilated and filled with the white calcareous masses. Microscopically, the pancreatic tissue showed considerable fibrosis, fatty degeneration and chronic

inflammation, with almost total lack of functioning pancreatic tissue (figs 3 and 4). The kidneys revealed glycogenic degeneration.

COMMENT

The first case of pancreatic lithiasis in the literature was reported by de Graff in 1667 (cited by Seeger^{2a}). He made no mention of associated glycosuria. In 1788 Cawley³ reported a case of pancreatic lithiasis in which the patient had had diabetes mellitus during life. He

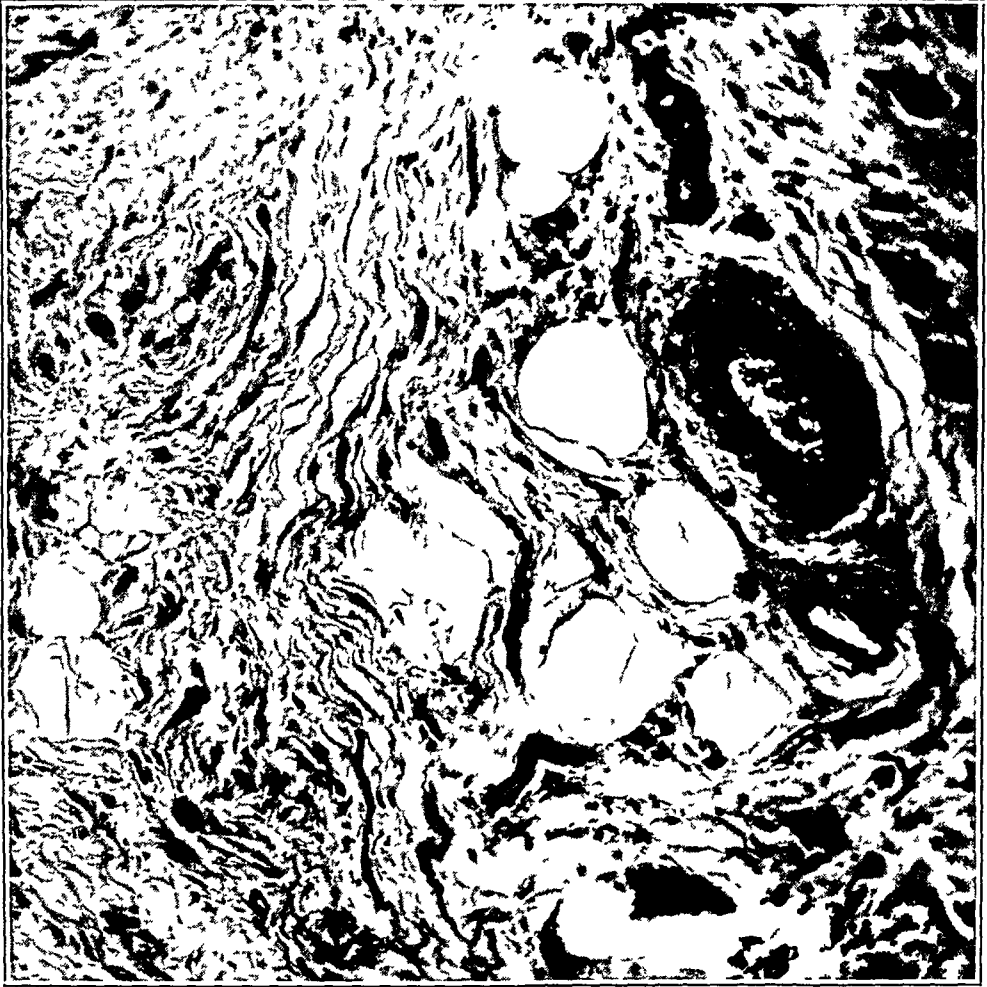


Fig 4—Microscopic section of the pancreas in case 2, illustrating extreme fibrosis with chronic interstitial inflammation and fatty invasion of the substance of the pancreas.

was the first to associate stones in the pancreas with diabetes. It remained for von Mering and Minkowski⁴ in 1889 to demonstrate for

2a Seeger, S. M. Pancreatic Lithiasis, *Radiology* **10** 126, 1928.

3 Cawley, T. A Singular Case of Diabetes, Consisting Entirely in the Quality of the Urine, with an Inquiry into the Different Theories of That Disease, *London M. J.* **4** 289, 1788.

4 von Mering, J., and Minkowski, O. Diabetes mellitus nach Pankreasexstirpation, *Arch. f. exper. Path. u. Pharmacol.* **26** 371, 1889-1890.

the first time the true relationship between the pancreas and diabetes. It is interesting to note that Banting received the initial stimulation for his epoch-making discovery of insulin by reading the report of a case of pancreatic lithiasis made by Barron in 1920.⁵ Barron reiterated what had previously been said by Opie,⁶ that stones cause atrophy of the gland but that the islands of Langerhans remain intact, glycosuria being found only in the event that interstitial pancreatitis develops.

Among 7,402 necropsies performed at the Cincinnati General Hospital between Jan 1, 1927 and Jan 1, 1938, there were noted but 3 instances of pancreatic lithiasis. One of the patients had been admitted to the hospital in diabetic coma, the second had a fracture of the skull, and the third had lobar pneumonia. The last 2 patients had no history of previous glycosuria. In 1903 Oser⁷ reported 70 cases of pancreatic lithiasis, in 24 of which glycosuria was demonstrated. Dillon⁸ examined the autopsy records in 2,800 cases at the Philadelphia General Hospital and found only 2 cases of pancreatic lithiasis.

In 1936 Dr J G Mayo⁹ found a total of 25 proved cases of pancreatic lithiasis in the records of the Mayo Clinic. In 2 of these, the correct diagnosis was made during the life of the patient, and was confirmed at operation in the first case and at autopsy in the second. In 14 cases the lithiasis was discovered incidentally in the course of operations for other conditions. In 9 cases the diagnosis was made post mortem.

The cause of pancreatic lithiasis has not been determined with certainty. It has been stated that stasis plays an important role. Experiments on animals in which the main duct was tied did not result in the formation of stones. Nearly all of the stones that are found in the pancreas are composed of calcium carbonate. The secretion of the pancreas does not contain calcium carbonate, and for this reason it is thought that some factor, probably infection, alters the secretion, thus bringing about the formation of stones. The stones are usually found in the ducts and sometimes in cysts, in abscesses or scattered throughout the entire gland. Mayo⁹ divided pancreatic stones into two types: first, true stones occurring in the ducts, and second, false stones repre-

5 Barron, M. Relation of Islets of Langerhans to Diabetes, *Surg, Gynec & Obst* **31** 437, 1920.

6 Opie, E L. Diabetes Mellitus Associated with Hyaline Degeneration of the Islands of Langerhans of the Pancreas, *Bull Johns Hopkins Hosp* **12**:263, 1901.

7 Oser. Disease of the Pancreas, in Nothnagel, H. *Practical Diseases of the Liver*, Philadelphia, W B Saunders Company, 1903, vol 3, pp 11-303.

8 Dillon, E S. Report of Two Cases Showing Glycosuria Following Obstruction of the Pancreatic Ducts, *Bull Ayer Clin Lab* **8** 35, 1924.

9 Mayo, J G. Pancreatic Calculi, *Proc Staff Meet, Mayo Clin* **11** 456, 1936.

senting calcification of the parenchyma following pancreatitis. He stated the belief that disease of the biliary tract is the causative agent in most cases. About 75 per cent of the cases reported have occurred in men. The largest solitary stone found was 2.5 inches (6.4 cm) in diameter.

Of the symptoms, the most important and most common is pain. The pain is present in the epigastrium, sometimes to the right and sometimes to the left of the midline and often radiates posteriorly. Many patients complain of pain apparently similar to that which occurs in biliary colic. Colicky epigastric pain was present in 19 of 29 cases collected by Ackman and Ross.¹⁰ During the attacks of pain, the patients often have diarrhea, the stools are light tan, greasy and spongy, and contain much grossly undigested food. These attacks may be accompanied by nausea and vomiting. Nearly all the patients complain of loss of weight. In a few cases jaundice has been found. Studies of enzymes have revealed marked diminution in pancreatic ferments. Other observations reported include stones in the stool, cutaneous pigmentation, a palpable mass in the epigastrium and a history of duodenal ulcer. These conditions do not occur with sufficient frequency to be of much diagnostic significance.

Roentgen examination is the most important aid in making the diagnosis during the life of the patient. In some cases the stones cannot be visualized, thereby making diagnosis difficult. Careful roentgen examination of the abdomen during visualization studies of the gallbladder would aid in making the diagnosis more frequently. Since many of the patients complain of pain similar to that in disease of the gallbladder, the taking of roentgenograms is usually limited to the right upper quadrant of the abdomen. In such cases the diagnosis may be missed. On the other hand, a flat roentgenogram of the abdomen taken before the administration of barium sulfate will usually reveal any stones which may be present in the pancreas. As pointed out by Hoechstetter,¹¹ the presence of an opaque medium, such as barium, in the stomach and intestines almost entirely obscures the site of the pancreas, hence the importance of taking a roentgenogram before the administration of the opaque meal. Stones in the region of the pancreas must be differentiated from renal lithiasis, calcified lymph nodes and cholelithiasis. It is of interest that in spite of the clear demonstration of the stones by a roentgenogram, it may be impossible to visualize them with the fluoroscope, even after their exact location is known. We observed this to be true in our first case.

10 Ackman, F. F., and Ross, A. Pancreatic Lithiasis, *Surg, Gynec & Obst* 55:90, 1932.

11 Hoechstetter, S. Pancreatic Lithiasis, *Am J Roentgenol* 37:33, 1937.

Contrary to the common belief that surgical treatment of this condition is fraught with danger, only 2 of 26 patients operated on died. In neither of these cases was fat necrosis or peritonitis the cause of death.^{2a}

SUMMARY

Approximately 125 cases of pancreatic lithiasis had been reported in the literature before 1939. Two cases are presented in this report. The signs and symptoms of pancreatic lithiasis may simulate closely those of disease of the gallbladder. The diagnosis was made during the life of the patient in 1 case and at autopsy in the other. Diagnosis may be made more frequently during life by careful roentgen examination of the abdomen before the administration of barium.

THE LEVEL OF IODINE IN THE BLOOD

H J PERKIN, M A

AND

FRANK H LAHEY, M D

BOSTON

Roger's "Practica," written about 1170, prescribed ashes of sponge and seaweed for goiter,¹ yet knowledge of the therapeutic value of iodine products in treatment of this disease and of the metabolism of iodine within the body has been developed only within the present century. Clinical and experimental evidence points to the fact that one of the primary functions of the thyroid gland concerns the metabolism of iodine. It is essential, therefore, to acquire as great an insight as possible into the biochemistry of iodine in normal and in goitrous persons. Investigations of the level of iodine in the blood have yielded information of value. The present communication deals with the development of knowledge of the concentration of iodine in the blood together with an analysis of a series of values for blood iodine in 1,078 consecutive patients with clinical hyperthyroidism and in 745 persons without evidence of thyrotoxicosis.

The quantitative estimation of the iodine content of the blood is not an easy procedure. This fact is evident from the numerous methods of analysis in the literature.² Many investigators experience difficulty in applying the method outlined by another worker and accordingly

From the Research Foundation and the Department of Surgery, the Lahey Clinic

1 Garrison, F H. *An Introduction to the History of Medicine*, ed 3, Philadelphia, W B Saunders Company, 1922, pp 141-142

2 (a) Bourcet, P. *Recherche et dosage colorimetrique de petites quantités d'iode dans les matieres organiques*, *Compt rend Acad d sc* **128** 1120-1122, 1899. (b) Hunter, A. *The Determination of Small Quantities of Iodine with Special Reference to the Iodine Content of the Thyroid Gland*, *J Biol Chem* **7** 321-349, 1909. (c) Blum, F, and Grutzner, R. *Methoden der Jodbestimmungen in organischen Substanzen*, *Ztschr f physiol Chem* **85** 429-470, 1913. (d) Kendall, E C. *Determination of Iodine in Connection with Studies in Thyroid Activity*, *J Biol Chem* **43** 149-159, 1920. (e) McClendon, J F. *The World's Supply of Iodine in Relation to the Prevention of Goitre*, *Science* **56** 269-270, 1922. (f) von Fellenberg, T. *Das Vorkommen der Kreislauf und der Stoffwechsel des Jods*, *Ergebn d Physiol* **25** 176-363, 1926. (g) Leitch, I, and Henderson, J M. *The Estimation of Iodine in Food Stuffs and Body Fluids*, *Biochem J* **20** 1003-1007, 1926. (h) Pfeiffer, G. *Ueber ein neue Schnellbestimmung von organisch gebundenem Jod*, *Biochem Ztschr* **195** 128-133, 1928. (i) Kuhn, P, and Loeser,

devise a modified or a new technic. In some instances simplicity and rapidity have been the reasons for developing another method. In estimating the iodine content of the blood, one of two principles is usually followed. The first is referred to as the open combustion method

A Einfache Schnellmethode zum quantitativen Nachweis von organisch gebundenem Jod in Körperflüssigkeiten, *Arch f exper Path u Pharmacol* **131** 262-267, 1928 (j) Jochman, E. Ein Beitrag zur von Fellenbergschen Jodbestimmungsmethode, *Biochem Ztschr* **194** 454-460, 1928 (k) McClendon, J F. The Determination of Traces of Iodine, *J Am Chem Soc* **50** 1093-1099, 1928 (l) Lunde, S, and Closs, K. Determination of Iodine in Blood *Norsk mag f lægevidensk* **89** 500-506, 1928 (m) Pincussen, L, and Roman, W. Gemeinsame Bestimmung der Halogene in organischen Substanzen, *Biochem Ztschr* **207** 416-429, 1929 (n) Reith, J F. Die Mikrobestimmung von Jodiden neben anderen Salzen, *ibid* **216** 249-268, 1929 (o) Glimm, E, and Isenbruch, J. Ueber die Bestimmung kleinster Jodmengen, *ibid* **207** 368-376, 1929 (p) Turner, R G. A Micro Colorimetric Method for the Quantitative Estimation of Iodine in Blood, *J Biol Chem* **88** 497-511, 1930 (q) Aitken, A A. Improved Method for the Determination of Iodine in Blood, *Biochem J* **24** 1456-1459, 1930 (r) Scheffer, L. Mikro-jod-bestimmung in organischen Substanzen, *Biochem Ztschr* **228** 426-436, 1930 (s) Schwaibold, J, and Harder, B. Die Bestimmung des Jods in biochemischen Materialien, *ibid* **240** 441-453, 1931 (t) Remington, R E, McClendon, J F, and von Kolnitz, H. The Determination of Traces of Iodine. Further Refinements in Technic, *J Am Chem Soc* **53** 1245-1249, 1931 (u) Elmer, A W. Zur Vereinfachung der Mikrojodbestimmung, *Biochem Ztschr* **248** 163-167, 1932 (v) Davis, C B, and Curtis, G M. The Quantitative Determination of the Iodine Content of Blood, *J Lab & Clin Med* **18** 24-29, 1932 (w) Baumann, E J, and Metzger, N. The Determination of Iodine in Blood, Foods and Urine, *J Biol Chem* **98** 405-416, 1932 (x) Allot, E N, Dauphinee, J A, and Hurtle, W H. The Determination of Small Quantities of Iodine in Blood, *Biochem J* **26**:1665-1671, 1932 (y) Widman, E. Die Methodik der Blutjodbestimmung, *Biochem Ztschr* **254** 223-228, 1932 (z) Leipert, T. Die Bestimmung kleinster Jodmengen inorganischen Material, *ibid* **261** 436-443, 1933 (a') Perkin, H J. Determination of Iodine in Blood, *Biochem J* **27** 1078-1081, 1933 (b') Eyckerman, J. Eine Mikrobestimmungsmethode des Jods im Blut und anderen flüssigen oder verflüssigten organischen Produkten, *Ztschr f Kinderh* **54** 435-439, 1933 (c') Phillips, F J, and Curtis, G M. Blood Iodine Studies. IV. The Clinical Determination of Iodine in Blood, Urine and Feces, *Am J Clin Path* **4** 346-353, 1934 (d') McCullagh, D R. A New Method for the Determination of Iodine, *J Biol Chem* **107**:35-44, 1934 (e') Harvey, C O. Determination of Iodine in Biological Substances, Medical Research Council, Special Report Series, no 201, London, His Majesty's Stationery Office, 1935 (f') Trevor, V, and Fashena, G J. The Determination of Iodine in Biological Material, *J Biol Chem* **110** 29-38, 1935 (g') Wilmanns, H. Zur Methodik der Mikrojodbestimmung in biologischen Material, *Biochem Ztschr* **289** 41-51, 1936 (h') Hamilton, R H. Improvements in Technic for the Determination of Microgram Quantities of Iodine, *J Am Chem Soc* **58** 1592-1594, 1936 (i') Fashena, G J, and Trevor, V. A Note in the Determination of Iodine in Biological Material, *J Biol Chem* **114** 351-355, 1936 (j') Stevens, C D. Determination of Iodine in Biological Material, *J Lab & Clin Med* **22** 1074-1079, 1937

Procedures employing open combustion are held in disfavor by some workers because of the susceptibility to loss of iodine and to contamination from the environment.³ The second principle is recognized as the closed system, the destruction of the organic material being done within a closed chamber. Methods involving the latter system have likewise been the subject of criticism.⁴ It is not our purpose to detail the advantages or the shortcomings of either principle. In approximately 25,000 analyses of blood iodine we have used an open combustion method^{2a'} and have found it to be satisfactory for our purposes. We believe that any investigator who will carefully adhere to the technic of any of the so-called standard procedures for determining the iodine content of the blood can obtain results which are relative one to another.

In 1900 Gley and Bourcet,⁵ using Bourcet's method,^{2a} demonstrated the presence of iodine in the blood of dogs. Using a liter of blood for analysis, they secured an average value of 5.5 micrograms per hundred cubic centimeters. The accuracy of this figure is recognized. Gallard,⁶ using the same method, studied the level of iodine in the blood of rabbits after the application of iodine to the skin. In 1914 Blum and Grutzner⁷ expressed doubt of the existence of iodine as a normal constituent of the blood of human beings. Cameron⁸ in 1914 and 1915, using the method of Hunter,^{2b} was unable to detect iodine in the blood of dogs and of rabbits. These negative results can be attributed to the small amount of blood (0.5 Gm.) used for a single estimation. Twenty years after Gley and Bourcet's original discovery, Kendall and Richardson⁹ confirmed the presence of iodine in blood. Using 100 Gm. of blood from dogs for analysis, they reported an average value of 13 micrograms per hundred grams.

From this work it was evident that iodine occurred naturally in normal blood. However, the large amount of blood required for one determination was a drawback in studying the level of blood iodine in human beings. This obstacle was overcome by von Fellenberg, who

3 Mobius, W. Vergleichende Blutjoduntersuchungen bei trockener und feuchter Veraschung, *Biochem Ztschr* **253** 275-278, 1932.

4 Doering, H. Die Blutjodwerte, *Biochem Ztschr* **280** 442-447, 1935.

5 Gley, E., and Bourcet, P. Presence de l'iode dans le sang, *Compt rend Acad d sc* **130** 1721-1724, 1900.

6 Gallard, F. Sur l'absorption de l'iode par la peau et sa localisation dans certains organes, *Compt rend Acad d sc* **128** 1117, 1899.

7 Blum, F., and Grutzner, R. Kommt Jod im Blut vor? *Ztschr f physiol Chem* **91** 450-464, 1914.

8 Cameron, A. T. Contributions to the Biochemistry of Iodine. The Distribution of Iodine in Plant and Animal Tissues, *J Biol Chem* **18** 335-379, 1914, **23** 1-39, 1915.

9 Kendall, E. C., and Richardson, F. S. Determination of Iodine in Blood and Tissues, *J Biol Chem* **43** 161-170, 1920.

reported in 1926^{2f} the first micromethod by means of which the quantity of iodine in 10 cc of blood could be estimated. The development of this technic was a stimulus to other investigators, and many studies on blood iodine appeared in the literature. Probably the most comprehensive of these was the work by Veil and Sturm,¹⁰ which showed that the average level of blood iodine in normal human beings was 12.8 micrograms per hundred cubic centimeters in the summer and 8.3 micrograms per hundred cubic centimeters in the winter. This observation was confirmed by Maurer and Diez,¹¹ and further evidence of a seasonal variation in the level of iodine in the blood was reported by Nitzescu and Binder¹² and Davis, Curtis and Cole¹³. On the other hand, Scheringer¹⁴ was unable to discern a seasonal variation in the iodine content of the blood, although he noted that a dietary deficiency of iodine resulted in a decrease in the iodine in the blood. These findings were in keeping with the work of Seidell and Fenger,¹⁵ who had previously reported a seasonal variation in the iodine content of the thyroid gland of animals. Jansen and Robert¹⁶ reported the normal range of values for blood iodine in human beings to be from 12 to 14 micrograms per hundred cubic centimeters, they noted that from 70 to 90 per cent of the total blood iodine was in the plasma. In a monograph on the biochemistry of iodine Orr and Leitch¹⁷ reported normal values for blood iodine to be from 6 to 8.4 micrograms per hundred cubic centimeters. Certain of these studies were the subject of criticism by Blum¹⁸.

10 Veil, W. H., and Sturm, A. Beitrage zur Kenntnis des Jodstoffwechsels, *Deutsches Arch f klin Med* **147** 166-223, 1925

11 Maurer, E., and Diez, S. Untersuchungen uber das Vorkommen von Jod in menschlichen und tierschen Organismus, *Munchen med Wchnschr* **73** 17, 1926

12 Nitzescu, I. I., and Binder, E. Iodemie normale. Variations saisonnieres, iodemie des goitreux, *Compt rend Soc de biol* **108** 279-280, 1931

13 Davis, C. B., Curtis, G. M., and Cole, V. V. Blood Iodine Studies. II. The Normal Iodine Content of Human Blood, *J Lab & Clin Med* **19** 818-830, 1934

14 Scheringer, W. Beitrag zur Kenntnis des Blutjodspiegels beim Weibe unter physiologischen Bedingungen, *Arch f Gynak* **143** 319-337, 1930

15 Seidell, A., and Fenger, F. Seasonal Variations in the Iodine Content of the Thyroid Gland, *J Biol Chem* **13** 517-526, 1912-1913

16 Jansen, W. H., and Robert, F. Die Jodfrage beim Kropfproblem, *Deutsches Arch f klin Med* **157** 224-246, 1927

17 Orr, J. B., and Leitch, I. Iodine in Nutrition, Medical Research Council, Special Report Series, no 123, London, His Majesty's Stationery Office, 1929

18 Blum, F. Gebt es einen von der Schilddruse abhangigen Jodspiegel des Blutes? *Schweiz med Wchnschr* **8**:808-813, 1927

Some interest has been taken in the physiologic variations of the level of iodine in the blood. Maurer and Diez,¹⁹ Maurer²⁰ and Scheringer¹⁴ reported that an increase in blood iodine occurred at the menstrual period in normal women. Maurer²⁰ noted an elevation in the blood iodine during the later stages of pregnancy. Bokelman and Scheringer²¹ concurred with this observation. In addition, Scheringer²² reported that an iodine-free ovarian extract was capable of increasing the iodine content of the blood. Hirsch²³ stated the belief that the periodic fluctuations in blood iodine in menstruating women were indicative of a thyroid-ovarian relation. Leipert²⁴ stated that the normal blood iodine level was 13 ± 4 micrograms per hundred cubic centimeters, irrespective of sex, age or season. He also stated that the blood iodine level in women was influenced by menstruation and pregnancy. A cyclic excretion of iodine in the urine of menstruating women has been reported by Cole and Curtis²⁵. Presumably this reflects a fluctuating level of iodine in the blood. With the apparent existence of many minor fluctuations in the level of iodine in blood, the exactitude of such physiologic variations remains to be established. In our studies, although variations in the iodine content of the blood of individual persons have been observed and attributed to season, to the menses or to pregnancy, such observations are not consistent to the degree that they may be considered applicable in all instances.

With certain factors effecting minor changes in the level of iodine in the blood, the greatest deviation from normal was believed to occur in patients with clinical hyperthyroidism. Veil and Sturm¹⁰ observed that the blood iodine in cases of exophthalmic goiter varied from 21 to 70 micrograms per hundred cubic centimeters. Bulmann,²⁶ reported a

19 Maurer, E, and Diez, S. Zur Kenntnis des Jods als biogenes Element, Ueber Wachstums beschleunigung an jungen Ratten bei Verfütterung jodangereicherter Kost an das laktierende Muttertier, *Biochem Ztschr* **182** 291-300, 1927. Scheringer¹⁴

20 Maurer, F. E. Ueber den Jodgehalt des Blutes und seine Veränderungen in Menstruation und Gravidität, *Arch f Gynak* **130** 70-79, 1927.

21 Bokelman, O., and Scheringer, W. Beitrag zur Kenntnis der Schilddrüsenfunktion und des Jodstoffwechsels in der Gestation, *Arch f Gynak* **143** 512-536, 1931.

22 Scheringer, W. Experimentelle Beeinflussung des Jodstoffwechsels durch Corpus-luteum-Hormon, *Arch f Gynak* **146** 248-260, 1931.

23 Hirsch, O. Ueber Beziehungen zwischen Eierstock und Schilddrüse bei der Basedowischen Krankheit, *Deutsches Arch f klin Med* **171** 44-51, 1931.

24 Leipert, T. Zur Kenntnis des physiologischen Blutjodspiegels, *Biochem Ztschr* **270** 448-454, 1934.

25 Cole, V. V., and Curtis, G. M. Cyclic Variations in Urinary Excretion of Iodine in Women, *Proc Soc Exper Biol & Med* **31** 29-30, 1933.

26 Bulmann, G. Iodine Contents of Blood Especially in Exophthalmic Goiter, *Hospitalstid* **74** 395-404, 1931.

series of values for blood iodine in normal persons and in patients with nontoxic goiter and with hyperthyroidism. Although an overlapping in the range of the results for the different groups existed, Bulmann's observations indicated that the estimation of the iodine in the blood was of value in the diagnosis of thyrotoxicosis. Nuernbergk and Widmann²⁷ stated the belief that the blood iodine level was elevated in all patients with disturbances of the vegetative nervous system, including exophthalmic goiter. Schittenhelm and Eisler²⁸ reported a consistent elevation of the blood iodine level of from 15 to 90 micrograms per hundred cubic centimeters in patients with exophthalmic goiter. They also noted an elevation in the blood iodine of normal persons after the injection of epinephrine, whereas in patients with exophthalmic goiter the findings were reversed. Breitner²⁹ observed an increase in blood iodine in patients with hyperthyroidism, and in these patients the seasonal variation was the converse of that previously reported for normal persons.¹⁰ Curtis, Davis and Phillips³⁰ concluded from their studies that a relation existed between the level of blood iodine and the degree of activity of the thyroid gland. Curtis, Cole and Phillips,³¹ Elmer and Schepps,³² Scheffer and von Megay,³³ Sturm, Plotner and Maas,³⁴ McCullagh,³⁵ and McCullagh and McCullagh³⁶ presented evidence favoring the diagnostic significance of estimating the blood iodine in diseases related to the thyroid gland. From the aforementioned work, the general impression prevailed that the blood iodine level was consistently elevated in patients with thyrotoxicosis despite the lack of correlation with the increment in the basal metabolic rate.

27 Nuernbergk, H., and Widmann, E. Blutjoduntersuchungen bei Vegetativ-Stigmatisierten, *Klin Wchnschr* **10** 1712-1713, 1931

28 Schittenhelm, A., and Eisler, B. Der Blutjodspiegel in seiner pathologisch-physiologischen und klinischen Bedeutung, *Klin Wchnschr* **11** 6-9, 1932

29 Breitner, B. Blutjodwerte und Jahreszeit, *Munchen med Wchnschr* **79** 513-514, 1932

30 Curtis, G. M., Davis, C. B., and Phillips, F. J. Significance of the Iodine Content of Human Blood, *J. A. M. A.* **101** 901-905 (Sept. 16) 1933

31 Curtis, G. M., Cole, V. V., and Phillips, F. J. The Blood Iodine in Thyroid Disease, *West J. Surg.* **42** 435-488, 1934

32 Elmer, A. W., and Schepps, M. The Iodine Content of Blood and of Urine and the Basal Metabolic Rate. Their Value in the Diagnosis of the Function of the Thyroid Gland, *Acta med. Scandinav.* **82** 126-136, 1934

33 Scheffer, L., and von Megay, L. Jodstoffwechsel bei Kropfträgern, *Klin Wchnschr* **14** 1360-1362, 1935

34 Sturm, A., Plotner, K., and Maas, K. Zur Blutjodfrage, *Biochem. Ztschr.* **280** 396-412, 1935

35 McCullagh, D. R. Studies in Blood Iodine by the Use of a New Chemical Method, *Cleveland Clin. Quart.* **2** 15-37, 1935

36 McCullagh, E. P., and McCullagh, D. R. Clinical Experiences in the Use of Determinations of Blood Iodine, *Arch. Int. Med.* **57** 1061-1066 (June) 1936

In contrast to the views previously stated, Turner³⁷ reported normal values for blood iodine in 5 (one third) of 15 cases of clinical hyperthyroidism. Veil and Sturm¹⁰ had previously noted the presence of normal blood iodine in 3 patients with exophthalmic goiter, the results were attributed to treatment with digitalis and quinine. More recently Perkin, Brown and Lang³⁸ and Perkin, Lahey and Cattell³⁹ observed the regular occurrence of normal values for blood iodine in about 30 per cent of all cases of clinical hyperthyroidism. Perkin⁴⁰ presented additional evidence to indicate that patients with thyrotoxicosis whose blood iodine content was normal were usually more refractory to surgical treatment. Somewhat later Perkin and Hurxthal⁴¹ and Perkin and Cattell⁴² reported a greater tendency to recurrent hyperthyroidism after subtotal thyroidectomy in patients with exophthalmic goiter who had a normal blood iodine level prior to operation.

Since in clinical hyperthyroidism (exophthalmic goiter and adenomatous goiter with hyperthyroidism) an increase in the level of iodine in the blood is usual, a subnormal level might be anticipated in patients with myxedema. Although results on a large group of cases are lacking, Curtis, Cole and Phillips,³¹ Elmer and Schepps,³² and Sturm, Plotner and Maas³⁴ have reported low values for blood iodine in patients with this condition. It would seem that the determination of the level of iodine in the blood is of questionable significance for diagnostic purposes in cases of myxedema because normal persons without evidence of thyroid insufficiency but with a subnormal blood iodine level are often observed. The fact that the average value for blood iodine in patients with myxedema is appreciably less than the average in normal persons is evidence favoring a relative deficiency of iodine-containing products secreted by the thyroid gland in this condition.

As an increase in the urinary excretion of iodine usually reflects an increase in the level of iodine in the blood, certain results of

37 Turner, R. G. Iodine Content of Certain Pathological Bloods in a Goitrous Region, *Proc Soc Exper Biol & Med* **29** 1294-1296, 1932.

38 Perkin, H. J., Brown, B. B., and Lang, J. Blood Iodine Content of Normal and Thyrotoxic Individuals. Iodine Tolerance Test, *Canad M A J* **31** 365-368, 1934.

39 Perkin, H. J., Lahey, F. H., and Cattell, R. B. Blood Iodine Studies in Relation to Thyroid Disease. Basic Concept of the Relation of Iodine to the Thyroid Gland, Iodine Tolerance Test, *New England J Med* **214** 45-52, 1936.

40 Perkin, H. J. The Value of Blood Iodine Estimations in the Treatment of Clinical Hyperthyroidism, *S Clin North America* **16** 1509-1511, 1936.

41 Perkin, H. J., and Hurxthal, L. M. The Blood Iodine Level Before and After Subtotal Thyroidectomy for Hyperthyroidism, *New England J Med* **215** 698-700, 1936.

42 Perkin, H. J., and Cattell, R. B. Blood Iodine Levels Related to the Recurrence of Hyperthyroidism, *Surg, Gynec & Obst* **68** 744-748, 1939.

determinations of the iodine content of urine are mentioned. The daily excretion of iodine in the urine of a normal person may be influenced by the daily regimen, the district in which the person lives and physiologic sex factors. Scheffer⁴³ noted an increased urinary excretion of iodine in untreated patients with hyperthyroidism. From his studies Scheffer concluded that thyrotoxic patients had a negative iodine balance. Curtis and Phillips⁴⁴ concurred with this observation. Elmer and Schepps³² reported that an increased excretion of iodine was present only in patients with severe hyperthyroidism. The problem has been studied more recently by Curtis and Puppel⁴⁵. Because of the limited stores of iodine in the body, it is difficult to conceive of a patient with clinical hyperthyroidism having a negative iodine balance indefinitely. In this connection we⁴⁶ presented evidence to show that the blood iodine level was usually elevated in patients with clinical hyperthyroidism who had had symptoms of thyrotoxicosis for nine months or less, after the symptoms of hyperthyroidism had persisted untreated for one year or longer, the blood iodine was generally observed to be normal. This observation, together with the previously mentioned studies on the urinary excretion of iodine, is in keeping with the results of chemical and histologic studies which have shown decreased amounts of iodine and colloid in the thyroid glands removed from untreated patients with exophthalmic goiter⁴⁷. Thus elevation of the blood iodine level and a concomitant increased urinary excretion of iodine would appear to be dependent on the presence and release of iodine from the thyroid gland. One might assume that the depletion of iodine from the thyroid gland of patients with exophthalmic goiter of long duration would result in spontaneous remission of the thyrotoxicosis. Although this is known to occur in some instances, we⁴⁶ have observed cases of severe, long-standing exophthalmic goiter in which no iodine was found in the blood and a negligible amount was excreted in the urine. The thyroid gland of such patients should be markedly deficient in iodine, but this fact could not be proved since iodine medication had

43 Scheffer, L. Ueber die Jodbilanz normaler Menschen, *Biochem Ztschr* **259** 11-18, 1933, Jodstoffwechsel bei Schilddrusekrankten, *Klin Wchnschr* **12** 1285-1286, 1933

44 Curtis, G. M., and Phillips, F. J. The Urinary Excretion of Iodine, *J Clin Investigation* **12** 963, 1933

45 Curtis, G. M., and Puppel, I. D. Increased Urinary Iodine in Hyperthyroidism, *Arch Int Med* **60** 498-508 (Sept.) 1937

46 Perkin, H. J., and Lahey, F. H. Exophthalmic Goiter. Relation Between the Blood Iodine Level and the Duration of Symptoms in Three Hundred and Five Cases, *Arch Int Med* **61** 875-879 (June) 1938

47 Cattell, R. B. The Pathology of Exophthalmic Goiter. Histologic and Chemical Changes Following Administration of Iodine, *Boston M & S J* **192** 989-996, 1925

been given prior to subtotal thyroidectomy. The basis of thyrotoxicosis in hyperthyroid patients who are depleted of iodine requires further elucidation.

The amount of iodine appearing in the urine should be dependent on the concentration of diffusible iodine in the blood. The inorganic iodine of the blood is derived chiefly from iodides, from the intestinal tract and from the end products of the metabolism of organic iodine which has been synthesized and secreted by the thyroid gland. As early as 1900 Gley and Bouicet⁵ dialyzed serum and found that most of the iodine present was nondiffusible. Since all the blood iodine was believed to be in the plasma or the serum, they concluded that it existed in protein combination. This was indeed an interesting observation for the time. Blum and Grutzner⁷ administered from 0.5 to 2 Gm. of sodium iodide to sheep and observed an increase of the iodine in the acetone extract of the blood. Veil and Sturm¹⁰ fractionated the iodine of the blood by precipitating the blood proteins with alcohol. The fraction insoluble in alcohol was called the organic blood iodine. The results of these investigators showed that from 60 to 70 per cent of the total iodine in the blood of normal persons and of patients with exophthalmic goiter was in the organic blood iodine fraction. The aforementioned work lent credence to the idea of an actual hypersecretion of iodine from the thyroid gland in patients with thyrotoxicosis. Pincussen and Roman⁴⁸ employed a method of electrodialysis to remove the inorganic constituents from the blood. Barkam and Leistner⁴⁹ separated the iodine fractions in blood by precipitating the inorganic fraction with silver and nitric acid. They noted that the administration of potassium iodide did not result in an increase in the organic iodine of the blood. Nuernbergk and Widmann²⁷ stated that the organic iodine in the blood was increased particularly in patients with exophthalmic goiter. Lunde, Closs and Pederson⁵⁰ used precipitation with alcohol followed by Soxhlet extraction to partition the iodine of the blood. They expressed the opinion that the nondiffusible iodine secured by their method constituted the active principle of the thyroid gland. They reported a relative decrease in the organic blood iodine following the oral administration of inorganic iodine in patients with hyperthyroidism, this decrease paralleled the decrease in the basal metabolic rate. Using similar methods of study,

48 Pincussen, L., and Roman, W. Ueber den Einfluss der Bestrahlung auf die Fraktionen des Jods und Broms im Tierkorper, besonders nach Zufuhr von Jodsalzen, *Biochem. Ztschr.* **216** 336-361, 1929.

49 Barkam, G., and Leistner, W. Das Verhalten des Jodes in den Korper-saften nach Verfutterung von Jodalkalien und Jodeiweiss, *Klin. Wchnschr.* **8** 117-118, 1929.

50 Lunde, G., Closs, K., and Pederson, O. C. Untersuchungen uber den Jodstoffwechsel, *Biochem. Ztschr.* **206** 261-274, 1929.

Dodds, Lawson and Robertson⁵¹ were unable to confirm these observations Nitzescu and Binder,¹² employing the fractionation method of Lunde and his associates,⁵⁰ reported the level of organic iodine in the blood to be relatively stable, with fluctuations occurring in the inorganic fraction From a theoretic standpoint, estimation of the organic iodine in the blood should be a closer index of the amount of thyroid secretion than assumptions based on analyses of the total blood iodine Such determinations should be of value for patients receiving iodine medication, provided that thyroid tissue alone has the capacity to synthesize organic iodine compounds One of the present difficulties is lack of experimental proof that with the methods of fractionation all the iodine products in the so-called organic iodine fraction which may be secreted by the thyroid gland are recovered This has been assumed by many investigators In this connection Trevorrow's⁵² studies on the nature of iodine in blood are of considerable interest It has been our experience that methods of blood iodine fractionation involving precipitation with alcohol recover, in the so-called organic blood iodine fraction, organic compounds of a molecular weight of 7,000 and greater⁵³ Thus thyroxine, if present in blood, would be recovered in the inorganic fraction In contrast, when the principle of dialysis for partition of blood iodine was used, specific amounts of thyroxine, when added directly to samples of blood, were mostly withheld in the nondiffusible fractions⁵⁴

An increase in the level of organic blood iodine in all patients with thyrotoxicosis seems doubtful,⁵³ although one must recognize that a relative increase may occur when the total blood iodine is still within normal limits No explanation can be offered for patients with clinical hyperthyroidism in whose blood no iodine can be demonstrated In patients with thyrotoxicosis the average values for the organic blood iodine may show a relative decrease after iodine medication The values are appreciably influenced by the amount and form of iodine administered and the time of analysis of blood iodine in relation to the previous dose of iodine When the nature of iodine in the blood and the influence of iodine medication on the organic iodine components of blood are more clear a definite understanding will be attained regarding the iodine metabolism in diseases of the thyroid

51 Dodds, E C , Lawson, W , and Robertson, J D Variations in the Iodine Content of the Blood in Hyperthyroidism and Nontoxic Goiter, *Lancet* **2** 608-611, 1932

52 Trevorrow V Studies on the Nature of the Iodine in Blood, *J Biol Chem* **127** 737-750, 1939

53 Perkin, H J , and Hurxthal, L M The Fractionation of the Iodine of the Blood in Thyroid Disease, *J Clin Investigation* **18** 733-737, 1939

54 Perkin, H J Unpublished data

Iodine medication in any form results in elevation of the level of iodine in the blood ⁵⁵ Veil and Sturm ¹⁰ noted that one and one-half hours after the oral administration of a single dose of iodine the maximum elevation in blood iodine occurred Elmer ⁵⁶ estimated the blood iodine level at specific intervals after the injection of 1,300 micrograms of iodine in the form of potassium iodide From the results he noted a difference in the blood iodine curves which was apparently related to the degree of thyroid activity as determined clinically A greater amount of iodine appeared in the blood of patients with hypothyroidism than in normal persons This observation was attributed to the inability of the thyroid gland to remove the administered iodine from the blood On this basis Elmer ⁵⁶ proposed an iodine tolerance test as an aid in the clinical diagnosis of hypothyroidism Perkin, Brown and Lang ³⁸ and Perkin, Lahey and Cattell ³⁹ reported a similar iodine tolerance test to facilitate in the diagnosis of clinical hyperthyroidism The level of iodine in the blood was determined at intervals after the oral administration of 72 mg of iodine (in the form of compound solution of iodine U S P) We ⁵⁷ later suggested that in so far as hyperplasia of the thyroid gland is associated with clinical hyperthyroidism this test ought to be of significance More recently Watson ⁵⁸ has added corroborative evidence to the aforementioned observations We have concluded that the iodine tolerance test is of more scientific interest than practical value The blood iodine curves secured from patients are often irregular and difficult to interpret This may be due to factors other than thyroid tissue affecting the blood iodine level during iodine medication ⁵⁹ However, the iodine tolerance test may still be used to advantage in isolated cases

It seems pertinent to mention that certain factors other than the thyroid gland may produce alterations in the level of iodine in the blood As these factors may play a role in the cause or in the effects of thyroid disease, they should be recognized by those interested in the

55 Perkin, H J, and Cattell, R B The Practicability and Significance of Blood Iodine Estimations, *New York State J Med* **36** 1033-1035, 1936

56 Elmer, A W Iodine Tolerance Test for Thyroid Insufficiency, *Endocrinology* **18** 487-496, 1934

57 Perkin, H J, and Lahey, F H The Iodine Tolerance Test as an Aid in the Diagnosis of Clinical Hyperthyroidism, *New England J Med* **216** 501-503, 1937

58 Watson, E M An Iodine Tolerance Test for the Investigation of Thyroid Function, *Endocrinology* **20** 358-362, 1936, The Relation of the Iodine Tolerance to Thyroid Function, *ibid* **22** 528-537, 1938

59 Perkin, H J, and Brown, B R The Influence of the Thyroid Gland and of the Ovary on the Metabolism of Iodine Experimental Study in Dogs, *Endocrinology* **22** 538-542, 1938

biochemistry of iodine in goitrous conditions Iodine in the diet in unsuspected forms (such as in sea food and iodized salt) affect the blood iodine level⁵⁵ Excessive amounts of calcium in the diet affect the blood iodine level in experimental animals⁶⁰ and may also exert an influence in human beings Iodine medication (administration of compound solution of iodine U S P orally, iodides intravenously, iodine preparations cutaneously or roentgen ray dyes orally or intravenously⁶¹) within one month prior to the analysis of blood iodine may result in an abnormal value Elevation of blood iodine may be found in patients with diseases of the liver and of the biliary passages⁶² In leukemia¹³ and in the early stages of acromegaly⁵⁴ there usually occurs an elevation in the level of iodine in the blood Most anesthetics⁶³ and all surgical procedures³⁵ result in an immediate increase in the blood iodine Strenuous exercise may increase the blood iodine slightly,³⁵ while complete rest usually causes it to fall As previously noted, variations in the level of iodine in the blood may be observed in women during the menstrual cycle and during pregnancy These variations in the level of blood iodine may or may not extend beyond the normal range for the method used One should bear in mind that a value at the upper normal limit may actually be an elevation of blood iodine for the particular person

Analyses of blood iodine were made on 1,823 persons In 745 persons who presented no clinical evidence of thyrotoxicosis (chart) the average (or mean) level of iodine in the blood was 6.8 micrograms per hundred grams The values for blood iodine ranged from 2 to 15 micrograms per hundred grams of blood, with 61 persons (8.2 per cent) having a value in excess of the upper normal limit by the method (10 micrograms per hundred grams) The results showed no significant variations attributable to age, sex or season It was found generally that normal persons of a vagotonic type had blood iodine values within the lower normal range On the other hand, normal persons of a sympathicotonic type were found usually to have blood iodine values within the upper normal range Since the same person varies in temperament, the level of iodine in the blood may fluctuate in a similar manner The correlation, however, could not be considered absolute

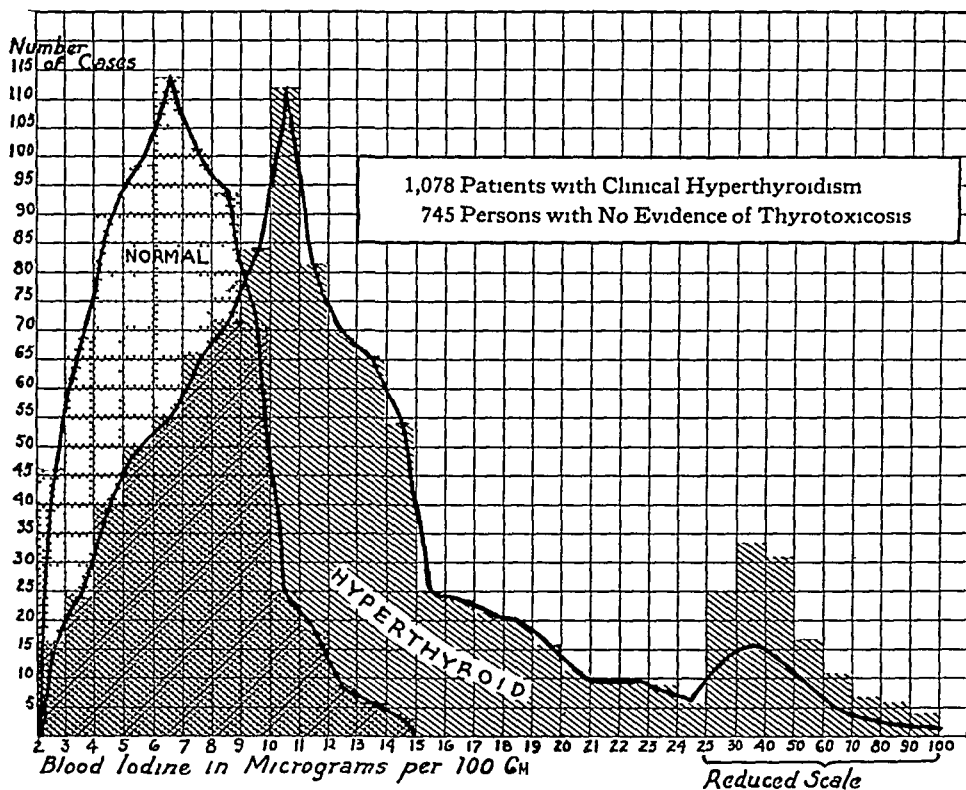
60 Thompson, I Influence of the Intake of Calcium on the Blood Iodine *Endocrinology* 20 809-815, 1936

61 Perkin and Cattell⁵⁵ Elmer⁵⁶ Veil and Sturm¹⁰

62 DeCourcy, J L Iodine Metabolism, Normal and Abnormal Its Relation to the Reticulo-Endothelial System, *Tr Am A Study Goiter*, 1937, pp 133-139 Perkin and Cattell⁵⁵

63 Anderson, W, and Leitch, I Effect of Anaesthetics on the Blood Iodine, *Lancet* 2 1391-1392 1927

The blood iodine values for 1,078 patients with clinical hyperthyroidism⁶⁴ are also shown. The average value for blood iodine was 15.5 micrograms per hundred grams. The mean level was considerably less, 11 micrograms per hundred grams. The range was from 2 to 100 micrograms per hundred grams. Approximately 34 per cent of the patients had blood iodine values of less than 10 micrograms per hundred grams. As previously pointed out, the presence in a specific case of an elevated or normal blood iodine value was roughly dependent on the duration of the hyperthyroid syndrome. Although the level of iodine in



Results of blood iodine analyses in 1,823 persons

the blood of patients with thyrotoxicosis may be influenced by states of excitement or of rest, the degree of variation was not as great as in normal persons. The ages of the patients under consideration ranged from 3 to 80 years, with no difference apparent in the effect of hyperthyroidism on the level of iodine in the blood.

In a review of the short history of investigations on the quantitative determination of iodine in blood, it is of interest that there has been a gradual decrease in the so-called normal blood iodine level. This transition reflects improvements in technical procedures together with a

64 No case in which iodine medication had been given within three months prior to examination was included.

better understanding of the sources of error in the methods for the microestimation of iodine. The development has been complemented by the availability of improved (iodine-free) chemicals. Baumann and Metzger⁶⁵ have pointed out that many of the earlier results of the estimation of iodine in the blood are too high. The ideas presented suggest the difficulty in determining the absolute amount of iodine in blood. However, the fact is not precluded that the results of determinations of iodine in the blood of different patients or of the same patient at different times are not relative one to another when estimated by the same method and by a worker familiar with the method. The relative blood iodine values have added considerably to the present conception of iodine metabolism in goitrous conditions.

⁶⁵ Baumann, E. J., and Metzger, N. On the Amount of Iodine in Blood, *J Biol Chem* **121** 231-234, 1937.

USE OF ALPHA LOBELINE FOR MEASUREMENT OF VELOCITY OF BLOOD FLOW

KURT BERLINER, M D
NEW YORK

Various methods for the measurement of the velocity of blood flow are now commonly employed. Most of them are subjective—they depend for their results on the cooperation of the patient, therefore, they not infrequently yield inaccurate results or fail altogether. The objective methods hitherto employed either are too complicated for ordinary clinical use or are potentially harmful to the patient. Recently the Russian authors Teplov and Sor¹ have suggested the use of alpha lobeline as an agent for the measurement of the velocity of blood flow. To my knowledge, this new, objective method for estimating “circulation time” has not yet been used in this country. I have undertaken, therefore, to investigate its merits, and I present the following preliminary report.

DESCRIPTION OF TEST

Technic—Prior to the test the patient is kept in a reclining position for about ten minutes. No preliminary instructions are given, and any remarks which might indicate the expected reaction are carefully avoided. Five milligrams of alpha lobeline hydrochloride (0.5 cc of the 1 per cent solution²) is rapidly injected into an antecubital vein. Several seconds later the patient experiences a choking sensation in his throat, comparable to that produced by the sudden inhalation of smoke. Usually this is accompanied by a grimace or a sudden start. Immediately thereafter the patient coughs. Hyperpnea may precede or follow the cough and may continue for one or two minutes. The time interval from the beginning of the injection to the onset of coughing, measured by a stopwatch, represents the “circulation time” for the patient. If cough fails to appear, the test is repeated with 7.5 mg of alpha lobeline hydrochloride ten to fifteen minutes later.

Principle of the Test—All methods for determining circulation time measure the time between the intravenous injection of an agent at one

From the Cardiological Department of Sydenham Hospital

1 Teplov, I, and Sor, V G. Graphic Method for Determining the Velocity of Blood Circulation by Means of Lobeline, *Terapark* **13** (no 2) 57-80, 1935

2 The ampules of alpha lobeline hydrochloride used in this study were supplied by the Sandoz Company

point and the perception of its effect at another point, the point of arrival. In the lobeline test, the latter point is the carotid sinus.^{2a} Lobeline has long been known to stimulate the respiratory center (Sollmann³) and thus to produce hyperpnea and cough. Recently, however, Heymans, Boukaert and Dautrebande,⁴ in experiments on animals, found that lobeline does not stimulate the respiratory center directly but that it acts on the carotid sinus, from which the respiratory center is stimulated by reflex action. "Lobeline circulation time," therefore, is "arm to carotid circulation time." To reach the carotid sinus, the injected lobeline travels from the antecubital vein by way of the subclavian vein, right side of the heart, lesser circulation, left side of the heart, aorta and carotid artery.

RESULTS

Two hundred and eighteen tests were made on 162 patients. In 151 patients (93 per cent) the circulation time was successfully determined by one or more tests. In 11 patients (7 per cent) the test failed to give the circulation time. Only 5 of these 11 had more than one injection, the remaining 6 were not available for repetition of the test. Had they been available, the percentage of failures would certainly have become less than 7 per cent.

Different amounts of alpha lobeline hydrochloride were used (table 1), 115 patients each received 5 mg. In 87 of these (76 per cent) the test was successful at the first attempt, in 28 (24 per cent) it failed. Of these 28 persons, 24 were available for repetition of the test. This was done, using 7.5 mg. of the drug in 11 instances (8 successes, 3 failures) and 10 mg. in 13 instances (10 successes, 3 failures). A second group of 58 patients, including the 11 just mentioned in whom the test with 5 mg. had failed, each received 7.5 mg. In 46 patients (79 per cent) the test was successful, in 12 (21 per cent) it failed. Furthermore, 16 persons were given a test with 10 mg., after smaller doses had failed, and in 10 of the 16 the circulation time was then obtained. Only 11 patients were given 11 to 13 mg. after smaller doses had failed, and in 8 of these the circulation time was at last obtained.

The 162 patients varied in age from 14 to 75, 82 were men and 80 were women. Of the 151 patients for whom circulation time was obtained, 33 were free from demonstrable cardiac disease, their circu-

2a An additional site of attack of alpha lobeline, perhaps in the bronchial wall, may exist. This possibility is suggested by the fact that very low figures for circulation time (five seconds) are occasionally obtained with this test.

3 Sollmann, T. A Manual of Pharmacology, ed. 4, Philadelphia, W. B. Saunders Company, 1932, p. 424.

4 Heymans, C., Boukaert, J. J., and Dautrebande, L. Sinus carotidiens et actions stimulantes respiratoires de la nicotine et de la lobeline, *Compt. rend. Soc. de biol.* **106**:469 1931, **109**:56 1932.

lation time varied from five to twelve and one-half seconds, with an average of eight and one-half seconds. Seventy patients were suffering from various types of heart disease but did not show any signs of cardiac failure, their circulation time varied from seven to eighteen seconds, with an average of ten seconds. Lastly, 43 patients were suffering from cardiac disease with congestive heart failure, their circulation time varied from seven to forty-six seconds, with an average of nineteen seconds. These results are summarized in table 2. With few exceptions, the results of the lobeline test corresponded quite well to the clinical estimations of the degree of cardiac failure. However, detailed comparisons have been deferred until a time when a larger number of patients will have been tested.

TABLE 1—*Effectiveness of Various Doses of Alpha Lobeline*

	Amount of Alpha Lobeline Hydrochloride			
	5 Mg	7.5 Mg	10 Mg	11 to 13 Mg
Total number of tests	115	58	16	11
Successful tests	87 (76%)	46 (79%)	10	8
Failures	28 (24%)	12 (21%)	6	3

TABLE 2—*Relation of Alpha Lobeline Circulation Time to Cardiac Disease*

	No Cardiac Disease	Cardiac Disease Without Signs of Congestive Failure	Cardiac Disease With Signs of Congestive Failure
Total number of patients	35	78	49
Number of patients in whom circulation time was obtained	33	74	44
Average circulation time	8½ sec	10 sec	19 sec

COMMENT

Teplov and Sol¹ suggested the use of 0.03 to 0.04 mg of alpha lobeline per kilogram of body weight of the patient. Their usual dose, therefore, was less than 3 mg. They made 300 tests on 165 persons and produced cough in 60 to 70 per cent. I began by using 3 mg doses for a series of 37 patients, not included in the present study, and as a result I had 15 failures (41 per cent). It soon became apparent that body weight was only a minor factor in determining the amount of alpha lobeline necessary to produce cough. Age, sex and, especially, individual variations in nervous irritability appeared to be much greater factors than weight. Women reacted more markedly than men and required smaller doses. Young persons required smaller amounts than old persons. Apprehensive persons responded to smaller amounts than did quiet, well controlled persons.

These conclusions from my experiences were supported by an analysis of those instances in which the test failed completely. If weight were the most important factor, the majority of these patients should have been heavy. Instead, of the 9 patients in whom doses of 10 to 12 mg of alpha lobeline failed to produce cough, none were stout, the heaviest weighed 158 pounds and the lightest, 138. All 9 were men. Only 1 of them (his age was 38) was below 40 years of age, 3 were above 60 years of age.

Demonstrable impairment of cerebral function seemed to inhibit somewhat the action of alpha lobeline. Only 4 patients who were in comatose or stuporous states were included in this series. All of these patients required larger doses, 7.5 to 12 mg. The results obtained on these 4 patients were, on the average, higher than those obtained on the remaining patients. A separate investigation is under way to determine how impairment of cerebral function by disease or by drugs affects the result of the lobeline test.

*Untoward Reactions*⁵—None of the 218 tests resulted in any injury to the patient. There were, however, certain unpleasant by-effects. The majority of the patients merely complained of a mild choking sensation, "as if fumes had gotten into the throat." Sometimes a patient gave a sudden start several seconds after the injection, put a hand to the throat as if to seek relief from a constriction and then coughed more or less violently a few seconds later. Other patients merely swallowed visibly or grimaced slightly before the cough began. One or two later spoke of having experienced a strangling sensation. In several instances, especially when 7.5 mg was used without a previous test with 5 mg, the patient was considerably frightened by the sensation in the throat. On the other hand, many patients experienced no choking sensation whatsoever, and in the majority of patients it was so slight as not to frighten them. A few patients later stated that they had felt "light headed" or "faint."

The cough produced by alpha lobeline, which followed these various subjective sensations and which represents the real end-point of the test, varied from one clearing of the throat to a rather violent spell of coughing lasting two or three minutes. In 2 instances, again when 7.5 mg was injected without trial of a smaller dose first, the patient presented the picture of severe bronchospasm. These spells distressed and frightened the patients markedly, but fortunately were of short duration.

⁵ Stanojevic, L. Die Bestimmung der Kreislaufzeit mit Lobelin, *Ztschr f Kreislaufforsch* **30** 521, 1938. Evzlina, M. M. Lobeline in Determination of Velocity of Blood Circulation, *Vrach delo* **20** 113, 1938. Trimarchi, E. Sul metodo della lobelina per la misura della velocita circolatoria, *Riforma med* **54** 1407, 1938. Arillaga, F. C., and de Soldati, L. Determinacion objetiva de la velocidad circulatoria por la lobelina, *Semana med* **1** 453, 1939.

The occasional occurrence of such excessive effects of lobeline undoubtedly constitutes the chief disadvantage of the method. They seem, however, to be avoidable by proper regulation of the dose. Most of the unpleasant reactions were observed at the beginning of this work, when I used larger doses. I have since learned to vary the dose according to the age, sex and individual irritability of the patient. While 5 mg. was the amount I injected in the majority of experiments reported here, 3 mg. seems a safer initial dose, it is certainly to be recommended for all persons below 25 years of age, especially women, and also for all adults over 25 years who appear apprehensive or excitable. Whenever a patient must be kept at complete rest (as, for example, after myocardial infarction), the smaller dose, of 3 mg., is also indicated. In all such instances, rather than produce an unpleasant reaction I prefer to risk initial failure and if necessary to repeat the test, with a larger dose. Patients who failed to cough after the first injection never had a violent reaction to a second, larger dose. The best safeguard against such reactions, therefore, is the use of a smaller amount of alpha lobeline at the start.

None of the 218 injections had any irritating local effect, venous thrombosis, in particular, was never seen after an injection.

Possibility of Error —At first I was tempted to consider as end-points sudden movements of the patient's throat, grimacing and other indirect signs of the effect of alpha lobeline which occur earlier than cough or which may occur in the absence of cough. I soon gave up that practice, since it made the end-point subject to individual interpretation. A sharp, easily perceptible end-point is necessary if circulation time is to be measured with any degree of accuracy. Cough, or rather the onset of cough, represents such an end-point. Repetition of the test on the same patient proved the reliability of this technic by yielding the same result each time. Only once did the reliance on cough lead to an error. The patient coughed accidentally five seconds after the beginning of the injection, and a wrong time was obtained.

Another possibility of error may arise from the fact that the figures for circulation time will vary in the same patient if the amounts of alpha lobeline are varied. Larger amounts of the drug usually result in slightly lower figures for circulation time. Eight patients were given two successful tests on the same day, one with 5 mg. and the second with 7.5 mg. In 6 of the 8 experiments the second test yielded a lower figure for circulation time. The differences ranged from one-half second to seven seconds. Therefore, whenever tests are repeated for comparison, it is necessary to use exactly the same dose of lobeline each time. I found it practical always to record in the chart the amount of alpha lobeline used, together with the result of the test, for example, "Lobeline circulation time 9 seconds (5 mg. used)"

Contraindications—So far I have found only one definite contraindication to the use of the alpha lobeline test, namely, recent hemoptysis. On a patient suffering from mitral stenosis who presumably had had pulmonary infarction, the test was made inadvertently. Hemoptysis, which had ceased only the day before, promptly started again. Other possible contraindications, such as bronchial asthma or acute inflammatory conditions of the lung, may be found by future observation. Dyspnea per se, I found, is not a contraindication, some dyspneic patients stated that they actually felt better shortly after the test.

ADVANTAGES AND DISADVANTAGES

Advantages and disadvantages of the alpha lobeline test to determine circulation time may be briefly enumerated.

Advantages

1. The method is simple.
2. The result does not depend on the willingness or ability of the patient to cooperate.
3. The end-point, cough, is sharp and readily perceptible.
4. No injurious effect, either local (venous thrombosis) or systemic, has been noted.
5. Only a small amount of material, 0.5 cc., is required, the duration of the injection, therefore, is short.
6. Lobeline has no cumulative effect, the test may be repeated after fifteen minutes.

Disadvantages

1. There is a possibility of unpleasant reactions (choking sensation, excessive cough, fright).
2. It is frequently necessary to repeat the test because the initial dose has been too small.
3. Complete failure may occur.
4. Results vary slightly with the amount of alpha lobeline used.
5. Results possibly may be influenced by processes of cerebral origin—for example, coma.

CONCLUSIONS

1. The alpha lobeline test is a practical method for the measurement of the velocity of blood flow.
2. Age, sex and individual variations in nervous irritability are major factors in determining the minimum amount of alpha lobeline required to produce cough, body weight is only a minor factor.

RETICULOENDOTHELIAL CYTOMYCOSIS

(HISTOPLASMOSIS OF DARLING)

ARTHUR A HUMPHREY, M D

BATTLE CREEK, MICH

A fatal disease so rare that in the third of a century following the original description only 4 cases of it were reported should merit only a passing or academic interest. However, when 5 other cases of the disease, which is a definite clinical entity, appear in southern Michigan in the course of a few months a new diagnostic problem is unquestionably thrust on physicians.

Darling,¹ in 1906, was the first to note in smears and sections taken at autopsy from the viscera of a Negro who had died at the Ancon Hospital in the Canal Zone a peculiar coccus-like organism which packed the endothelial cells. In the ten months after the first case he observed the same histologic picture in the cases of 2 other residents of Panama.² Clinically, the syndrome (splenomegaly, irregular pyrexia and leukopenia) resembled that of kala-azar, and the microscopic appearance was so similar to that of kala-azar that, although he found no typical Leishman-Donovan bodies, Darling felt that the new organism must be protozoan in character, he therefore called it *Histoplasma capsulatum*³ and applied the name "histoplasmosis" or "reticuloendothelial histoplasmosis" to the disease. In 1934, however, De Monbreun⁴ demonstrated that a fungus was the etiologic factor, and, since the old term was misleading, he suggested the name "cytomycosis" for the disease. For the sake of pathologic description, although with some sacrifice to brevity, I would retain the prefacing "reticuloendothelial," for the reticuloendothelial system, almost alone, is the portion of the body involved.

From the Leila Y Post Montgomery Hospital Laboratory

1 Darling, S T. A Protozoan General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen and Lymphnodes, J A M A **46** 1283 (April 28) 1906

2 Darling, S T. Histoplasmosis. A Fatal Infectious Disease Resembling Kala-Azar Found Among the Natives of Tropical America, Arch Int Med **2**. 107 (Sept) 1908

3 Darling, S T. The Morphology of the Parasite (*Histoplasma Capsulatum*) and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, J Exper Med **11** 515, 1909

4 De Monbreun, W A. The Cultivation and Cultural Characteristics of Darling's *Histoplasma Capsulatum*, Am J Trop Med **14** 93 (March) 1934

After Darling's reports, no further cases of what was considered a rare tropical disease were noted until 1926, when Watson and Riley⁵ reported the case of a woman who had been a resident of Minnesota for over forty years. In the same year Phelps and Mallory⁶ described a case in Honduras, and in 1931 a second case in the United States was described.⁷ In 1934 Dodd and Tompkins⁸ reported the first case in which diagnosis was made during life, on the basis of blood smears. This was the case of an infant in Tennessee. The first cultural studies of the organism were made in this case by De Monbreun.⁴ These workers found that it was possible to observe the organisms in blood smears prepared with Wright's stain but that supravital preparations stained with neutral red were much superior.

Recently 5 cases of the disease have been observed in a limited area in Michigan. Amolsch,⁹ in Detroit, has described 1, 2 have been noted in the department of pathology at the University of Michigan¹⁰ (the characteristic organisms were seen only in an adrenal and a lymph gland, respectively) and I have performed necropsies in 2 cases within twenty-five miles of Battle Creek. Oddly, the autopsies in these last 2 cases were performed but forty-eight hours apart.

REPORT OF CASES

CASE 1 (Patient of Dr. A. B. Gwinn, Hastings, Mich.)—S. R., a white youth aged 17, was admitted to the Pennock Hospital on Aug. 23, 1937, because of a persistent infection of the upper respiratory tract which in the few days prior to entry had developed into pneumonia. His condition was not considered serious, and he immediately started to improve, but he remained in the hospital because a profound leukopenia was discovered during the routine laboratory examination.

His health had been excellent prior to the present illness, with the exception of a fungous infection in one ear in 1935. He had been born and had lived in northern Indiana until he was 1½ years of age, since that time he had lived in a small city in central Michigan. There was no history of suspicious medication which might have depressed the production of leukocytes.

5 Riley, W., and Watson, C. J. Histoplasmosis of Darling. Report of a Case Originating in Minnesota, *Am J Trop Med* **6**: 271 (July) 1926. Watson, C. J., and Riley, W. A. A Case of Darling's Histoplasmosis Originating in Minnesota, *Arch Path* **1**: 662 (April) 1926.

6 Phelps, B. M., and Mallory, F. B. Toxic Cirrhosis and Primary Liver Cell Carcinoma Complicated by Histoplasmosis of the Lung, in *Fifteenth Annual Report of the Medical Department of the United Fruit Company*, New York, United Fruit Company, 1926, p. 115.

7 Crumrine, R. M., and Kessel, J. F. Histoplasmosis (Darling) Without Splenomegaly, *Am J Trop Med* **11**: 435 (Nov.) 1931.

8 Dodd, K., and Tompkins, E. H. A Case of Histoplasmosis of Darling in an Infant, *Am J Trop Med* **14**: 127 (March) 1934.

9 Amolsch, A. L., and Wax, J. H. Histoplasmosis in Infancy, *Am J Path* **15**: 477 (July) 1939.

10 Parsons, R. J. Personal communication to the author.

On the day of admission the physical findings, with the exception of those associated with the mild pneumonia, were essentially negative. The hemoglobin content of the blood was 70 per cent (Sahli), there were 3,750,000 erythrocytes per cubic millimeter of blood and 1,900 leukocytes, of which 31 per cent were polymorphonuclear neutrophils and 69 per cent were lymphocytes. Later in the day the count was repeated and 1,600 leukocytes were found, with only 25 per cent polymorphonuclear cells. Urinalysis gave negative results.

Course—Pentnucleotide (30 cc) was given on the following day, and, although the leukocyte count did not increase, the percentage of granulocytes increased to 30. Over a period of eight days an additional 120 cc of pentnucleotide was given, and the white blood cell count rose slowly but steadily to 3,200, with approximately 40 per cent polymorphonuclear neutrophils on Sept 3, 1937. Treatment was then discontinued. The patient left the hospital on October 16, apparently in good health, the leukocytes numbered 4,500, and although the percentage of polymorphonuclears had previously reached a peak of 65, it was then 40, with 60 per cent lymphocytes.

The patient renewed his former life and graduated from high school in June 1938. On July 8 he was readmitted, a number of bullous lesions having appeared on his face and body. Stomatitis developed, from which Vincent's organisms were recovered. These lesions subsided after five days of sulfanilamide therapy. A blood count was made on July 8 which showed a hemoglobin content of 105 per cent, a red cell count of 5,000,000 and 4,000 leukocytes, of which 90 per cent were lymphocytes and 10 per cent were polymorphonuclear neutrophils.

Some ulceration of the roof of the mouth still existed when he was examined on August 29 by Dr. John D. Littig, and there were large masses of palpable glands, which appeared to be matted together on each side of the neck. Some involuted erythematous patches were still present on the face, and a small gland was palpable in the left axilla. The liver and spleen were not palpable. The temperature was 103 F and the pulse rate 105. He had severe anemia, with a hemoglobin content of 40 per cent (5.6 Gm) and a red cell count of 1,600,000. His leukocyte count was 3,150, with a differential count of 54 per cent small lymphocytes, 46 per cent large lymphocytes, one megaloblast and many normoblasts. The Kahn and heterophile tests were negative.

During the next six weeks he was given seven blood transfusions (500 cc each) and placed on a high caloric diet, with vitamin C and yellow bone marrow. Pentnucleotide was given twice daily until thirty-eight injections had been given. About October 1 his fever subsided, he was discharged from the hospital and was up and about at home. On October 5 it was found that his lymphadenopathy had disappeared. He complained of dysphagia and hoarseness, had lost 20 pounds (9 Kg) in weight and felt very weak. There were no physical findings of note at this time, and the liver and spleen were not palpable. The hemoglobin content was 64 per cent and the red blood cell count 3,400,000. The leukocytes numbered 2,700, one week later they fell to 2,075 with 18 per cent polymorphonuclears, 75 per cent lymphocytes and 7 per cent eosinophils in the differential count. The platelets, as in previous counts, appeared to be normal. On December 5 the leukocyte count reached 5,800, but the granulocytes varied between 3 and 30 per cent and the patient was obviously failing.

On Jan 9, 1939 the leukocytes had dropped to 1,500, with only 15 per cent polymorphonuclears. Roentgen therapy was then given over the long bones for three periods, with very obvious clinical improvement, and while the white blood cell count remained near 2,000, the percentage of polymorphonuclears increased to 55 by February 5. The patient was up and about at this time, but the anemia

again became marked, and purpura developed. On March 8 he was given two transfusions in the home. On the following morning he experienced a sudden loss of vision, lapsed into a coma and died within a few hours. A few days prior to death it had been believed that the liver was palpable but that the presence of what appeared to be ascites prevented definite assurance.

Necropsy (March 10, 1939) —The body was emaciated but well developed. The heart was slightly enlarged and lay free in a sac containing approximately 80 cc of clear straw-colored fluid. There were some firm white nodules, which measured between 3 and 6 mm in diameter, on the anterior surface of the left ventricle. A similar nodule, 2 mm in diameter, was also present on one of the papillary muscles in the interior of the ventricle, this nodule had a faint yellow tint. The pleural cavities contained small amounts of slightly cloudy fluid. The left lung was firmly adherent to the parietal pleura. The visceral pleurae of both lungs were dotted with small white nodules which were slightly raised or appeared as flat plaques. The surface of the liver showed nodules of the same type, which varied from pinhead size to 1 cm in diameter, and a few were scattered through the interior of the liver, on cross section they were white and were vaguely demarcated. The liver was enlarged 50 per cent and was yellowish brown in color. The spleen weighed approximately 700 Gm, small white plaques and nodules were scattered over its surface and on cross section it appeared dark red, with occasional small nodules of white on a firm smooth surface. There was about 400 cc of clear straw-colored fluid in the peritoneal cavity. With the exception of a few of the small white nodules on the peritoneal surface of the pylorus and duodenum, the gastrointestinal tract was essentially normal. The lymph nodes of the mesentery were enlarged, and a huge mass of lymph nodes, matted together, buoyed up the pancreas. On cross section, these nodes were yellowish and somewhat necrotic in certain areas. The adrenals were autolyzed. The kidneys were enlarged (30 per cent) and pale, and their capsules stripped readily.

Microscopic Study —Sections through the pleural nodules and through those from the interior of the lung showed masses of endothelial macrophages filled with small, coccus-like, dark-staining bodies with white halos or capsules about them. There were but a few in some cells, and they were densely packed in others. In some nodules there was marked central fibrosis and in others necrosis, in either event the periphery was dotted with intact or degenerating histiocytes filled with the organisms. In other nodules, where fibrosis was marked, there was no necrosis and few organisms were present. There was a marked infiltration of lymphocytes and plasma cells in this type of nodule, but in the other types there appeared to be no leukocytic reaction or response.

In the spleen packed histiocytes of the same type were scattered about, some of them were free in the sinuses. There were extensive areas of necrosis about some of the larger vessels, with many organism-packed cells in their outer zones.

Collections of the involved histiocytes were scattered more or less uniformly throughout the liver, some areas showed necrosis and a mild fibrosis. The hepatic cells contained a moderate amount of fat and some brown pigment granules and were somewhat distorted. Almost all of the Kupffer cells were involved and, although in many instances they were quite isolated from the large cell collections, were filled with the organisms.

In the cardiac musculature there were several large areas in which there were cells packed with organisms, numerous plasma cells and what appeared to be immature lymphocytes. These areas were often so extensive as to cover a

low power field In the renal tubules, with the exception of some granular degeneration, there was little change In about a third of the glomeruli, however, one or more cryptococcus-filled histiocytes were observed in the tufts (fig 1) Sections through the lymph glands showed marked necrosis, but few organisms were present The infiltration of plasma cells and lymphocytes was most pronounced in these enlarged nodes Sections through the pancreas showed an occasional organism-filled cell in the interstitial tissue, and many lymphocytes Sections through the intestinal wall showed nothing of note

Diagnosis—The diagnosis was reticuloendothelial histoplasmosis of Darling

CASE 2 (Patient of Dr D B Morrison, Tekonsha, Mich) —H S, a white man aged 46, was admitted to the Leila Y Post Montgomery Hospital on Feb 7, 1939 He complained of anorexia and weakness, which had become progressively worse

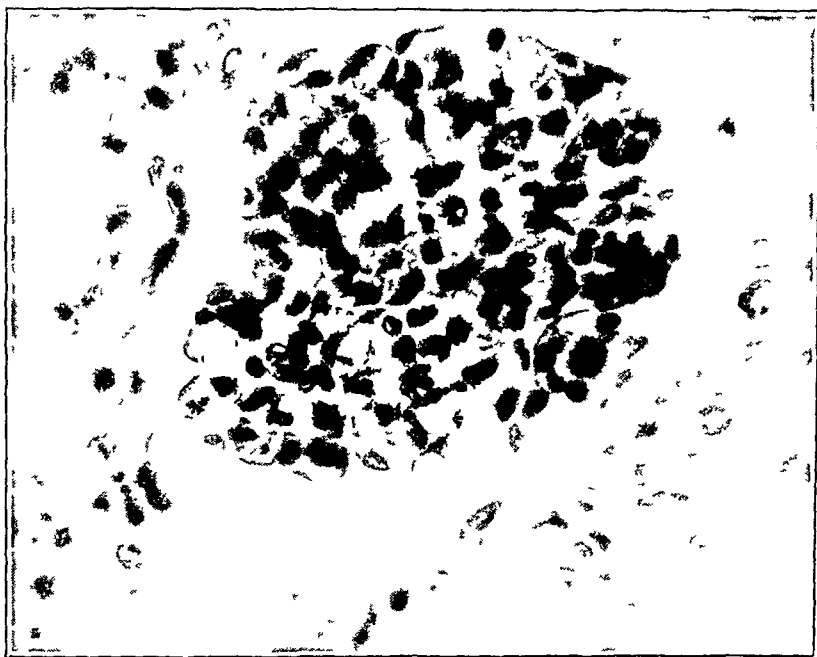


Fig 1—Glomerulus, four organism-filled cells enmeshed in the capillary tuft
× 300

since their onset in September 1938 In the previous three months he had lost 30 pounds (13.5 Kg) Since the last of December he had had several severe chills associated with bouts of fever and profuse sweats Recently he had been nauseated and had vomited frequently He had been forced to discontinue his farm work, although he experienced no pain and was perfectly comfortable if he remained in bed Recently there had also been some postprandial abdominal pain

The patient had always lived and worked on a farm in Michigan His past history was one of long-standing poor health He had suffered from colitis since childhood and had had an appendectomy in 1927 In 1919 a dog bite required several stitches, and the year following he had had a severe infection in one foot following a penetrating wound from a sharp stick His father died from nephritis, the remainder of the family history was essentially irrelevant

Physical examination revealed an emaciated man who weighed 110 pounds (49.5 Kg) and was 5 feet 6 inches (168 cm) in height He presented the picture of a chronic invalid, the slightest exertion required obvious effort The liver could

be palpated and had a smooth border extending slightly below the costal margin. At this time the spleen appeared to extend almost to the iliac crest, yet a few days later it could scarcely be palpated. No tenderness was present. The blood pressure was 120 systolic and 80 diastolic. He was deaf in the left ear.

A blood count on January 23 had revealed a hemoglobin content of 78 per cent, an erythrocyte count of 4,360,000 and a leukocyte count of 6,200. A differential count showed 44 per cent polymorphonuclear neutrophils, 43 per cent lymphocytes, 7 per cent eosinophils, 3 per cent monocytes and 3 per cent "stab" cells. On his entry into the hospital the hemoglobin reading (photometer) was 58 per cent. The red cell count was 3,380,000 and the white cell count 6,450, of which 64 per cent were polymorphonuclears, 24 per cent lymphocytes, 2 per cent monocytes and 8 per cent myelocytes. Smears showed marked polychromasia and anisocytosis and several megaloblasts and normoblasts. The Kahn, Widal and undulant fever agglutination tests were negative. A fractional gastric analysis revealed only a small amount of combined acid until after the first hour, when, after histamine, the free acid reached 12 degrees. Urinalysis gave negative results. Roentgen examination on February 8 demonstrated a normal stomach and duodenum. The hilum of the lungs were thickened, and there was some mottling in the lower pulmonary fields. Some enlargement of the liver and spleen was noted.

Course—From Jan. 22, 1939, when his case was first recorded, until his death, on March 10, 1939, his temperature varied between 102 and 105 F. in the afternoons and returned to normal in the evening.

During the five day stay in the hospital the temperature "spiked" between 102.2 and 104 F. The night sweats were drenching. Splenic puncture was attempted but was abandoned in accordance with the patient's wishes. Treatment consisted of four blood transfusions and solution of potassium arsenite U. S. P. He left the hospital unimproved on February 12. At home he became progressively weaker and more irrational, and he died on March 10.

Necropsy (March 11, 1939)—The embalmed body was emaciated. When the thoracic cavity was opened, a small amount of clear fluid was found in the left pleural cavity. The right lung was firmly adherent to the chest wall. In the apex of the left lung there were a number of nodules, gray or white in color and firm on cross section, the largest of which measured 8 mm. in diameter. There was, however, one spongy, dark reddish brown nodule, which measured 9 or 10 mm. in diameter. There were some calcified hilar nodules, and the lower lobes of both lungs were dark, heavy and noncrepitant. On cross section, there were noted an increase in fluid and a markedly decreased froth. The heart appeared normal.

Examination of the abdomen showed the liver to be normal in color and slightly enlarged, it was normal on section. The spleen was enormously enlarged (600 Gm.) and on cross section was dark red, with a smooth, even surface.

The gastrointestinal tract appeared to be normal, as did the gallbladder, adrenals and pancreas. The kidneys were normal in size but were bound together at the lower poles by a fibrous band 5 mm. thick and 2 cm. wide. The ureters arose from the lower poles of the kidneys and, with the pelves, lay far anterior to their usual position. The bladder and prostate were normal. The testes were small and on cross section did not "string."

Microscopic Study—Sections through the liver showed collections of histiocytes filled with cryptococci, numerous isolated reticuloendothelial cells were also involved (fig. 2). There was very little necrosis, and the liver cells, except for a small amount of fat in certain areas, appeared essentially normal. There were a few scattered lymphocytes but no polymorphonuclear cells.

Splenic sections showed areas of necrosis ringed about by the filled histiocytes. There was some fibrosis, and a few plasma cells and lymphocytes were present. There were some cells of the Steinberg type—small and with three or four superimposed nuclei centrally located in a dark cytoplasm. There were a few isolated cells filled with the coccus-like organism.

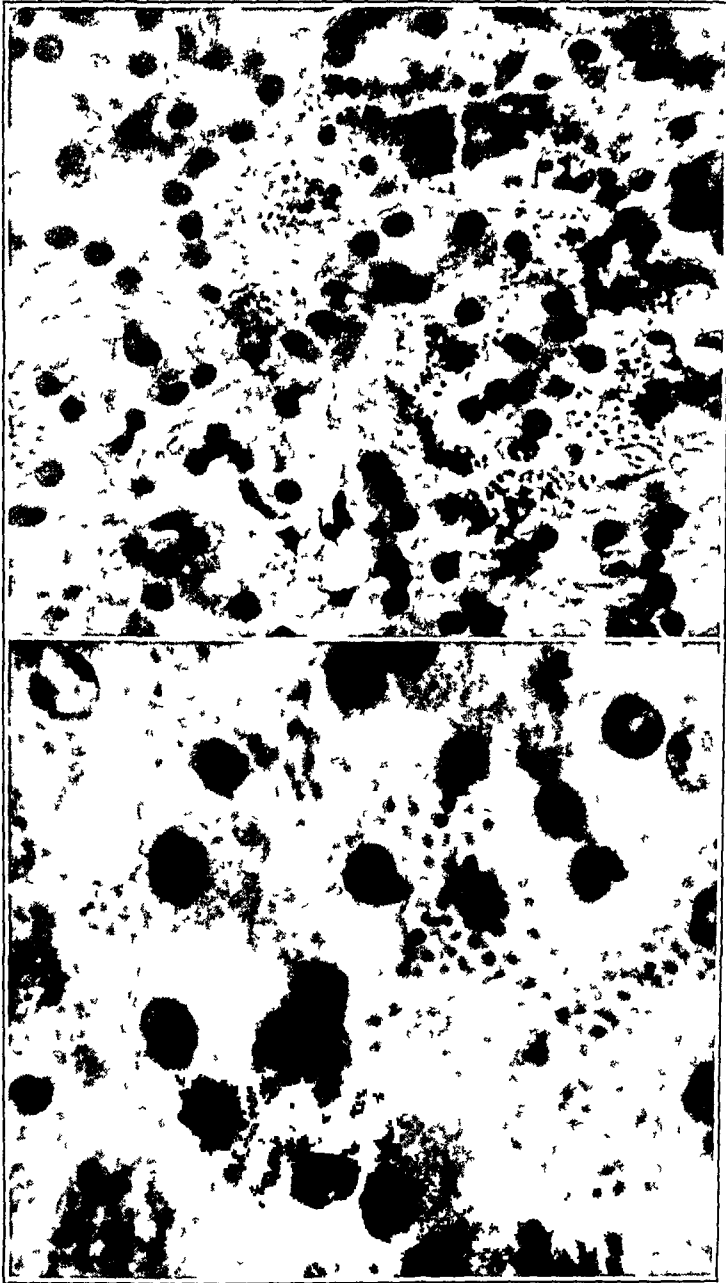


Fig 2—Sections of liver, histiocytes packed with the organism $\times 300$, $\times 800$

Sections through the kidney showed some tubular atrophy and an increase in connective tissue. There were some fibrous hyalinized crescents about the glomeruli, and some of the tufts showed one to a dozen isolated phagocytic cells filled with the organisms.

The glands removed from the hilus of the lung showed a typical healed tuberculous process, those from the abdomen, although not enlarged, showed the organism-packed histiocytes and the multinucleated cells with a large number of plasma cells

The small white nodules in the lung resembled those found in case 1, but the solitary brown nodule was a cavity filled with a tangle of mycelial strands (fig 3) There were no coccoid forms in or about it

No organisms were observed in sections of the heart or prostate

Diagnosis—The diagnosis was reticuloendothelial histoplasmosis of Darling, horseshoe kidney, bronchopneumonia, healed pulmonary tuberculosis

Comment on the Histologic Observations—While it may appear from the foregoing descriptions that the histologic sections in these cases resemble each other closely they actually do not In the first case a more general involvement was apparent even in microscopic section, and marked necrosis and fibrosis were

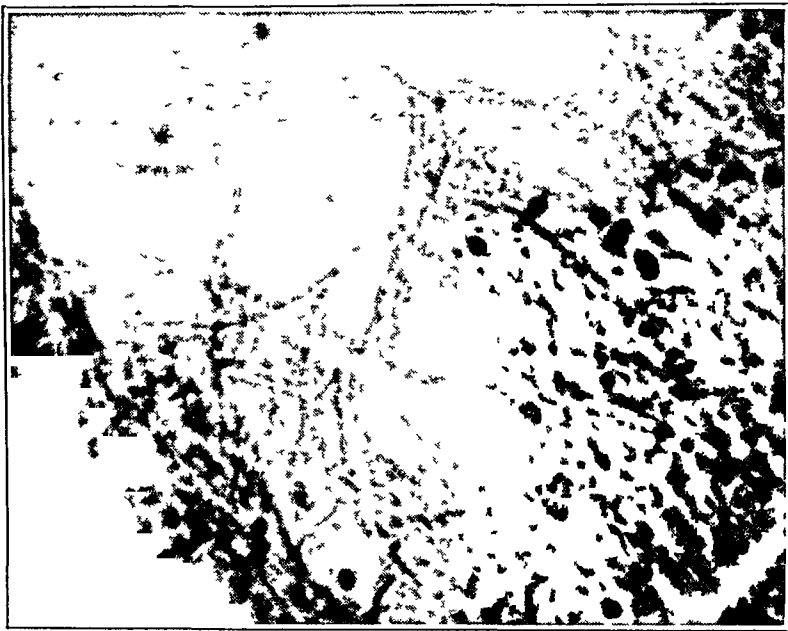


Fig 3 (case 2) —Mycelial form (?) of fungus in nodule from the lung $\times 300$

present In the second case there was very little necrosis and fibrosis, even in the liver, the cells in the involved areas being quite intact although collected in large sheets The liver showed marked changes in the first case, while in the second it appeared to be essentially normal in many areas except for the filled endothelial elements The general impression to be gained from a study of the sections was that in case 2 the disease was far less advanced and that only a few areas, such as the abdominal nodes, showed changes approaching those observed in case 1 It is possible that in these areas the disease had been present for a much longer period

The slide showing the mycelial elements was submitted to Dr Morris Moore,¹¹ of St Louis, who has made a thorough study of the mycologic aspect of this disease Because of the inadequacy of the preparation, he is hesitant to term the growth a mycelial phase of the yeastlike form found in the tissues but he has stated that he can see many points in common between the two organisms The

¹¹ Moore, M Personal communication to the author

fact that transition from one form to the other is seen in cultures and animal inoculation adds some weight to the possibility, if the transition is considered to be the result of a particular environment, at a particular point, which is favorable to change. Moore considers the intracellular bodies observed in the 2 cases here reported to be similar to the original *Histoplasma capsulatum*.

ETIOLOGIC CONSIDERATIONS

The causative organism is unquestionably a fungus. The studies of De Monbreun⁴ have since had the support of other mycologists who in 1934 were somewhat divided as to its exact taxonomic status, although the first impressions were that it belonged to the genus *Endomyces*. In cultures isolated from the spleen and blood in 1 case De Monbreun was able to cultivate the yeastlike form in which the organism was isolated and to convert it to the mycelial form at will, and then, by animal inoculation, to return it to the yeastlike phase. Monkeys inoculated with the cultures presented typical clinical symptoms, and at autopsy the pathologic appearance of the lesions was similar.

At one time *Cryptococcus farciminosus*, the causative agent of epizootic lymphangitis in horses, was suspected of being the guilty organism, but further studies absolved it. This organism closely resembles the so-called *Histoplasma capsulatum*, but cultural studies made differentiation possible, and the clinical symptoms of its presence in man are mild and local. Under moderate magnifications the tissue sections in cases of cytomycosis are also distinctly reminiscent of those of kala-azar, but there are no blepharoplasts and the distribution in the tissue is decidedly different.

Moore¹¹ has recently found the organisms in the prostate in the case of a patient from St. Louis and has had the opportunity of studying some referred cases (including 1 from Iowa City which has been reported by Hansmann and Schenken¹²). He feels that two closely related fungi are responsible for the disease, namely, *Histoplasma* (cryptococcus) *capsulatum*, as originally described by Darling, and also a piriform type. These two are quite easily distinguished by their clubbed terminations in the mycelial phase but apparently are indistinguishable in the yeastlike form. In my opinion, there is a very slight difference in the size of the organisms in the 2 cases reported here, this, however, can probably be attributed to the variant mediums in which they grew.

In case 2, sections of the small reddish brown nodule observed near the apex in one lung showed a luxuriant growth of a fungus in the myceliate state. If this mycelial formation is a second phase of the

12 Hansmann, G. H., and Schenken, J. R. A Unique Infection in Man Caused by a New Yeast-Like Organism, a Pathogenic Member of the Genus *Sepedonium*, *Am J Path* 10 731, 1934.

fungus present in the yeastlike phase in the same person, it is apparently the first time such a phenomenon has been observed. The mycelial growth bears some resemblance to De Monbreun's illustrations of his various cultures, but it lacks the ascus-like bodies he described.

The exact site of entry is uncertain, the skin has been suggested, with possible bites or infestations by parasites, as the mode of entry, but the portal most commonly accepted appears to be the lungs. They at least are the site of the oldest and most dense involvement in many cases, and in 1 case the organisms were observed only in the lungs, while pulmonary foci were absent in 2 cases, it is possible that in these the foci were too minute to be observed. In case 2 it is not difficult to imagine that the reason the myceliate form developed in one nodule in the lung might be that it had been the original focus and was therefore the only one to show this phase.

I think attention can be profitably drawn to the ear as a possible primary focus. In 1 of the cases previously reported otitis media was present during the disease and the organisms were found in the discharge,⁷ in another, there was otitis media,¹⁰ and in one of the present cases (case 1) the patient had been treated for a fungous disease of the ear shortly before the onset of the illness. The frequency with which various fungous infections invade the auditory canal also lends some weight to this suggestion.

PATHOLOGIC CHANGES

Descriptions of the gross and microscopic pathologic changes observed in this disease are somewhat discordant, and one recalls the predicament of the 3 blind men of Hindustan. Thus, in 1 case⁶ the lungs alone showed the organism in the endothelial cells, and since in this case the patient died from a far advanced visceral malignant process, we are forced to believe that a more general dissemination was prevented and that the disease in question was observed in a rather early stage, in other cases¹³ the engulfed blastospores were found only in the adrenal glands. Some of the data from the cases reported in the literature are presented in the table.

Grossly, the spleen appears to be almost invariably enlarged, in 1 case⁷ it weighed but 210 Gm and the authors emphasized that this was a variant to the usual pathologic picture. (However, I feel that a spleen of this size should be considered definitely enlarged.) Of the gross pathologic changes, next in frequency of incidence to splenomegaly are the small nodules (pinhead to pea size) which are observed in the lungs, liver and spleen, in that order of frequency. In more advanced

¹³ Currie, R. W., cited by Parsons¹⁰

Tabulation of Reported Cases

Author Date	Sex Age	Locality	Duration of Illness	Temperature, F	Spleen	Emaciation	Leukocyte Count	Red Cell Hemo Count, globin, Millions %	Other Findings
Darling 1905	M 27	Canal Zone	3½ mo	101	Palpable, large, 3 × normal at necropsy	Moderate	2,200	60	Colitis vomiting (3 mo)
Darling 1906	M 29	Canal Zone	? In hospital for 2 wk	101	Palpable 5 × normal				Headache, emesis, diarrhea
Darling 1906	M 55	Canal Zone (China 15 yr before)	5 mo	102	Enlarged and firm	Slight	Normal	70	
Watson and Riley 1925	F 52	Minnesota	8 yr	102	Large for 8 yr 10 × normal (liver large)	Weight loss of 35 lb over years	3,000 4,000 67% polys	3 8	Albuminuria, illness marked only last month
Phelps and Mallory 1926	M 24	Honduras	7 wk	101	Large (liver also large)	Marked	7,860	60	Carcinoma of liver, vomit ing
Crumrine and Kessel 1931	M 42	Louisiana and California	9 mo	101- 102 5	Nonpalpable ne- cropsy, 210 Gm	Weight loss of 33 lb in 6 mo	3,000 80% polys	3 12	Colitis 3 mo, epigastric pain weakness, cough
Dodd and Tompkins 1934	M 6 mo	Tennessee	3 wk	100	Palpable (liver also)		11,640, 22% P 63% L	2 07	Pus in middle ear icterus Index 30, early erythrocytes
Amolsch 1939	F 8 mo	Michigan	4 mo	101 103	Palpable ne- cropsy, 159 Gm	Marked	1,500, average 44 55% polys	2 00	Weakness, cough, otitis media, normoblasts
Humphrey 1939	M 18	Michigan	19 mo	103 remissive	Vague in life necropsy, 700 Gm	Moderate	1,200 3,500	1 72 5 2	Cough last month epis- taxis normoblasts
Humphrey 1939	M 46	Michigan	9 mo	102 5	Palpable ne- cropsy, 600 Gm	Marked	6,200	3 38	Weakness, sweats, nausea, vomiting, normoblasts

stages of the disease, however, the nodules are widely disseminated and appear in the intestine, on the peritoneal and pleural surfaces and even in the heart, as in 1 of my cases. They may be uniform or may vary in size, they may be white or pearly gray, and on cross section they may appear seminecrotic, firm or hyalinized. It is probable that these nodules exist in every tissue of the body in far advanced stages, and not, as once stated, only in the viscera rich in free histiocytes and reticuloendothelial elements. Most of these nodules appear hyalinized on section and undoubtedly represent a late phase of the histiocytic aggregations. Intestinal ulceration, sometimes resembling the amebic type, has occurred in several cases. An almost constant gross finding is peribronchial and abdominal perivertebral lymphadenopathy, many of the affected glands attain the size of hens' eggs and appear necrotic on cross section. In several cases the nodes about the jejunum and pancreas formed huge masses, which in 1 instance were palpable through the abdominal wall.

In the first case reported in this paper I felt that at autopsy I was dealing with a generalized sarcomatosis, and I marveled at the duration of life in the face of such a widespread involvement. In the second case the gross pathologic changes were disappointing, as actually the only thing of note was the large spleen and a few small hyaline plaques on the apical pleura of one lung, associated with adhesions of the type commonly observed in this area and with the calcified hilar nodes of healed tuberculosis on the same side.

It is apparent that the gross pathologic changes vary only as the duration or degree of dissemination of the disease may dictate and, as the microscopic study will demonstrate, probably have nothing to do with the resistance of the patient or with similar factors. In many respects the picture resembles the differences observed in the gross findings in patients with a malignant growth, thus, there may be a general miliary carcinomatosis, or, by contrast, only a few nodules in one or two organs.

Microscopically, the parasites occur in various phagocytic cells, such as the endothelial wandering cells of the tissues and the large mononuclear cells of the blood and marrow, as well as in the fixed reticuloendothelial cells of the liver and spleen (for example, the Kupffer cells of the liver). All observers appear to agree that the location of these yeastlike organisms is limited to the reticuloendothelial system and other phagocytic cells¹⁴ and that no other tissue is involved nor are adjacent cells damaged by any toxin from the organisms.

The yeastlike form measures 3 to 5 microns⁴ in diameter and consists of an oval or round dark-staining body surrounded by a clear,

¹⁴ Watson, C. J. The Pathology of Histoplasmosis (Darling) with Special Reference to the Origin of the Phagocytes, *Folia haemat* 37 70 (Oct.) 1928

halo-like capsule While other stains have been recommended, the organism can in most instances be observed and recognized with some degree of certainty with the high, dry objective of the microscope in sections stained with hematoxylin and eosin The bodies pack the phagocytic cells in numbers from 1 to 50, they show some variation in staining characteristics, due, no doubt, to degenerative changes

There appear to be three rather well defined types or stages of lesions First, there are areas in which isolated phagocytic cells are filled with parasites, or in which collections of these cells form small masses or sheets, such as are observed frequently in the liver Such isolated cells were present in the glomerular tuft of the kidney in the cases reported here Neither in the glomerulus nor in the liver does there appear to be a vestige of leukocytic reaction about these cells, and in most instances the untouched cells of the infested organ are unchanged This is doubtless the earliest phase of the invasion in a particular area The blood stream has carried one laden histiocyte to lodge in that site, and in a fruitless endeavor to share the burden, other uninvolved phagocytic cells have collected at this point These in turn become involved by direct extension, and thus a large sheet of these cells develop This is the probable explanation of the masses in the cardiac muscle, which are somewhat difficult to understand on any other basis

The second phase results in a somewhat different type of lesion The long-continued and progressive obstruction of the vessel conveying the original involved phagocyte to the area finally results in necrosis, this change is most marked in the center of the mass, and the phagocytes which have wandered peripherally in the surrounding tissue form a more or less intact ring about the caseating center In the sections of liver it is interesting to note the regular distribution of these areas In this phase the continued ischemia appears to affect some parenchymal cells, thus, in the liver the hepatic cells undergo changes and often show areas of fatty degeneration about the histiocytic mass

The third phase is the end result of necrosis Fibrous tissue and hyaline masses replace the lesion, and scarcely any laden phagocytes remain, the parasites which remain stain hypochromatically and probably are degenerating A few plasma cells and lymphocytes are scattered about, and mitotic figures are often observed In several instances multinucleated cells, which often resembled Reed, or Sternberg, cells, were observed, and even giant cells In the sections studied by me the cytoplasm of these cells was rather light, and the three or four nuclei were partially superimposed and semivascular

Obviously, these parasite-laden cells can migrate to any part of the body, and their absence in sections from certain organs must indicate

merely either failure due to random sampling or an early stage of the disease. It is also easily seen that the processes of early isolated histiocytosis, of caseation and of fibrosis or hyalinization can exist contemporaneously in the same patient, although one of the three phases may dominate the picture.

In certain areas fibrosis and hyalinization may reach such proportions that no organisms can be observed. The question is thus raised as to whether a complete cure might not be accomplished in the early stages of the disease.

SYMPTOMATOLOGY

The disease is apparently relentlessly progressive during its course, which may occupy only a few months or weeks, as in the cases of the 2 infants cited in the table, or eight years, as in another instance,⁵ there may be long remissions, or the disease may enter the acute phase and terminate rapidly.

Fever (temperature 100 to 105 F) was the most constant clinical finding, although in three of the reported cases the temperature returned to normal for extended periods. The fever was accompanied by pronounced loss in weight and extreme weakness.

Gastrointestinal upsets, such as diarrhea, nausea and vomiting, occurred in half of the cases, the diarrhea was often extremely severe. It is interesting that there was usually no definite pain.

Despite the pulmonary involvement the only related symptom was cough, present in 3 cases. Epistaxis occurred but once, and there was no hemoptysis. Death occurred usually as the obvious result of increasing inanition, although in 2 cases the finale was extremely rapid.

The spleen was palpable at some time during the course of the disease in most of the cases, occasionally enlargement of the liver was also noted. If one disregards the omnipresent emaciation, the only other significant physical finding encountered was a cervical or abdominal lymphadenopathy, and this in but a few cases. In 2 instances large nodes were palpable through the upper portion of the abdominal wall.

Laboratory findings were only rarely pathognomonic. In 1 instance the organism was noted in the blood smears and cultures, in another, the spleen was removed and the diagnosis was made from the sections of this organ. It is quite obvious, however, that in many instances splenic puncture would have been a valuable diagnostic procedure. Hyperbilirubinemia occurred in 2 cases and albuminuria in 3 others.

In the 7 cases in which the red cell counts were recorded a profound anemia of the aplastic type, probably a result of displacement of marrow, was noted. The number of erythrocytes varied from 3,800,000 to 1,700,000, with an average of 2,600,000, the hemoglobin content was from 35 to 85 per cent. Of 8 cases the white count was low at some

time during the disease in 5 (below 1,500 in 2), slightly elevated in 1 (11,640) and normal in 2. The differential counts showed normoblasts or megaloblasts in 4 cases, in some of these the anemia was not marked, and one is led to believe that it might be due to an irritative lesion of the marrow.

The ratio of lymphocytes to polymorphonuclear leukocytes varied during the course of the disease in certain cases and also among the various cases. Thus, in 1 case in which there was marked leukopenia the ratio was essentially normal, while in another a constantly recurring agranulocytosis appeared. It is apparent that the character of the blood count depends on the degree of involvement of the hemopoietic tissue by the organism.

DIAGNOSIS

The diagnosis can be made definite only by the detection of the fungus in the phagocytic cells of the blood, in smears from sternal or splenic punctures or in sections of tissue removed at splenectomy. It should be considered in cases in which there are continued fever, splenomegaly and leukopenia.

A severe anemia often occurs in the later stages, it may be hyperchromic and the presence of erythroblastic forms may be noted.

Leukopenic diseases, such as malaria, typhoid, kala-azar, malignant processes involving hemopoietic centers and certain phases of infectious mononucleosis and undulant fever, must be ruled out in the differential diagnosis.

PROGNOSIS, COURSE AND TREATMENT

The course, as has been stated, may be acute, terminating in a few weeks, or the process may extend, with irregular exacerbations or in a chronic form, over a period of years. The general impression is that the disease is invariably fatal, although in some of the recent cases it appears to be concomitant with some entirely unrelated disease which is the direct cause of death. It seems probable that in certain instances the lesions may remain in an arrested state for some time or, possibly, may undergo fibrosis, with a permanent cure as a result.

Treatment has been of no avail. Iodides, ionized metals, roentgen radiation, bone marrow, pentnucleotide and repeated transfusions have been only of transient value. There is no record of the use of sulfanilamide or its variants.

COMMENT

Two cases have been presented in which there were, fortunately, a detailed clinical history and a reasonably good follow-up and necropsy. The organisms were not cultured, however, nor were they observed during life. Luckily, in the 2 cases the disease was disseminated in two distinct phases, so that insight into the pathologic processes attendant

on its course was afforded. I have been able to establish a few facts relative to the pathology and diagnosis of reticuloendothelial cytomycosis by correlating the 7 previously reported cases with the present 2 and with 1 unpublished one.⁹ Prior to this time, the paucity and incompleteness of the material have prevented any but a very dubious clinical and pathologic concept. It is hoped that to the list of disorders characterized by pyrexia, splenomegaly and leukopenia another will now be added.

Six other cases have been noted within the last few months in the Mississippi River basin, in addition to the 3 recent ones mentioned, but to my knowledge these have not as yet been reported.¹⁵ The fact that 9 have occurred in the space of a year when only 7 had been catalogued in the preceding twenty-four years is both interesting and alarming. While the yeastlike form of the organism is not prominent in sections of tissue, neither is it so retiring as not to excite comment, I can scarcely believe that the present increase in the number of cases is due to improved diagnostic acumen alone. I do understand that in 2 cases the organisms were not noticed or identified for many months after the sections had been examined, but in the illustrations of the various cases and in my sections they are definite and cleancut oddities.

At first the disease was believed to be tropical, but although Muller a few years ago reported 1 case in Java,¹⁶ all of the recent reports have come from the central portion of North America. It is quite probable that in tropical regions the disease may be submerged by the similar syndromes of kala-azar and malaria so common in those regions, but some reason must exist for the rather abrupt appearance of the disease in the Mississippi River basin. One reason that suggests itself is the increased facility with which men now move from one climatic zone to another, thus the fungus or some parasite conveying it, in either the yeastlike or the mycelial form, may be carried for great distances by plane or automobile before the organism or carrier succumbs to the new environment.

Several articles on the experimental production of this infection in animals have appeared in the Italian literature, recently Redaelli¹⁷ has studied the rate of disappearance of congo red in the circulation in the disease. He describes a relationship between the concentration

15 De Monbreun, W. A. The Dog as a Natural Host for *Histoplasma Capsulatum*, *Am J Trop Med* **19** 565 (Nov) 1939.

16 Muller, H. Histoplasmosis in East Java, *Geneesk tijdschr v Nederl-Indie* **72** 889, 1931.

17 Redaelli, P. Osservazioni e considerazioni su alcuni aspetti anatomici e funzionale del sistema reticolo-istiocitario nella malattia sperimentale da *histoplasma capsulatum* Darling, *Riv di pat sper* **16** 1 (Jan-Feb) 1938.

of dye and the efficacy of the involved or hypertrophied reticuloendothelial system which may in the future be applied to the study of the disease in man

SUMMARY

Two cases of histoplasmosis of Darling are presented, the more apt name of reticuloendothelial cytomycosis is suggested, in accordance with the work of De Monbreun. Sufficient cases have now been collected to justify an effort to correlate the varied clinical and pathologic findings in a definite concept which will facilitate clinical diagnosis.

A clinical entity which prior to a year ago was considered a great rarity may become a common and serious problem and should be suspected in all cases demonstrating the not uncommon syndrome of pyrexia, splenomegaly and leukopenia.

It is suggested that increased facilities for transportation may be the cause of the recent increase in the number of cases.

Dr. John D. Littig, of Kalamazoo, Mich., and Miss Lorena Hilbert, of the Pennock Hospital Laboratory, Hastings, Mich., placed excellent records at my disposal.

ACUTE MILIARY INFARCTION OF THE HEART

JAMES R LISA, M D

AND

ELSIE McPEAK, M D

NEW YORK

This communication is a report of 99 cases of what we have called acute military infarction of the myocardium, the lesion was usually associated with the clinical syndrome of sudden left ventricular failure. The material reviewed consisted of 2,857 consecutive cases in which autopsies were performed at City Hospital during the twelve year period between 1927 and 1938, inclusive. These cases were first separated into two groups on the basis of the presence or absence, macroscopically, of moderate or marked sclerosis of the larger coronary

TABLE 1—*Classification of 2,857 Cases in Which Autopsy Was Performed*

Group	Total Number	Number in Which Acute Military Infarctions Were Present	Number in Which Acute Coronary Thrombosis Was Present
1 Cases in which coronary arteriosclerosis was present	983		
(a) Cardiac	336	51	42*
(b) Noncardiac	647	15	10*
2 Cases in which coronary arteriosclerosis was not present	1,874	9	0

* Of the 52 hearts with acute coronary thrombosis, 24 were studied histologically all these showed acute military infarctions

arteries. The group in which coronary sclerosis was present was subdivided into (a) those in which the primary clinical feature was cardiac dysfunction (cardiac-sclerotic group) and (b) those in which the presenting clinical syndrome was noncardiac (noncardiac-sclerotic group). Cases in which acute coronary thrombosis occurred were also grouped separately. The classification is summarized in table 1.

The most prominent characteristics of the acute military infarction were sharp definition, the tendency to concentrate on the left side of the heart and the predilection for the deep layers of the myocardium. As to size, the involved area about filled a low power field of the microscope, the shape of it was somewhat irregular (fig 1). At all stages the lesion was surrounded by well preserved myocardium. All phases of

From the Pathological Laboratory, City Hospital, Welfare Island, Department of Hospitals

necrosis of the muscle could be seen in various foci. In the early phase the fibers became granular. The granular appearance rapidly gave place to amorphous masses of cytoplasm. As the amorphous masses disappeared, the lipochrome became more prominent. Then the nuclei and the cytoplasm completely disappeared, leaving only the preexisting reticulum and traces of lipochrome (fig 2). The invading cells were

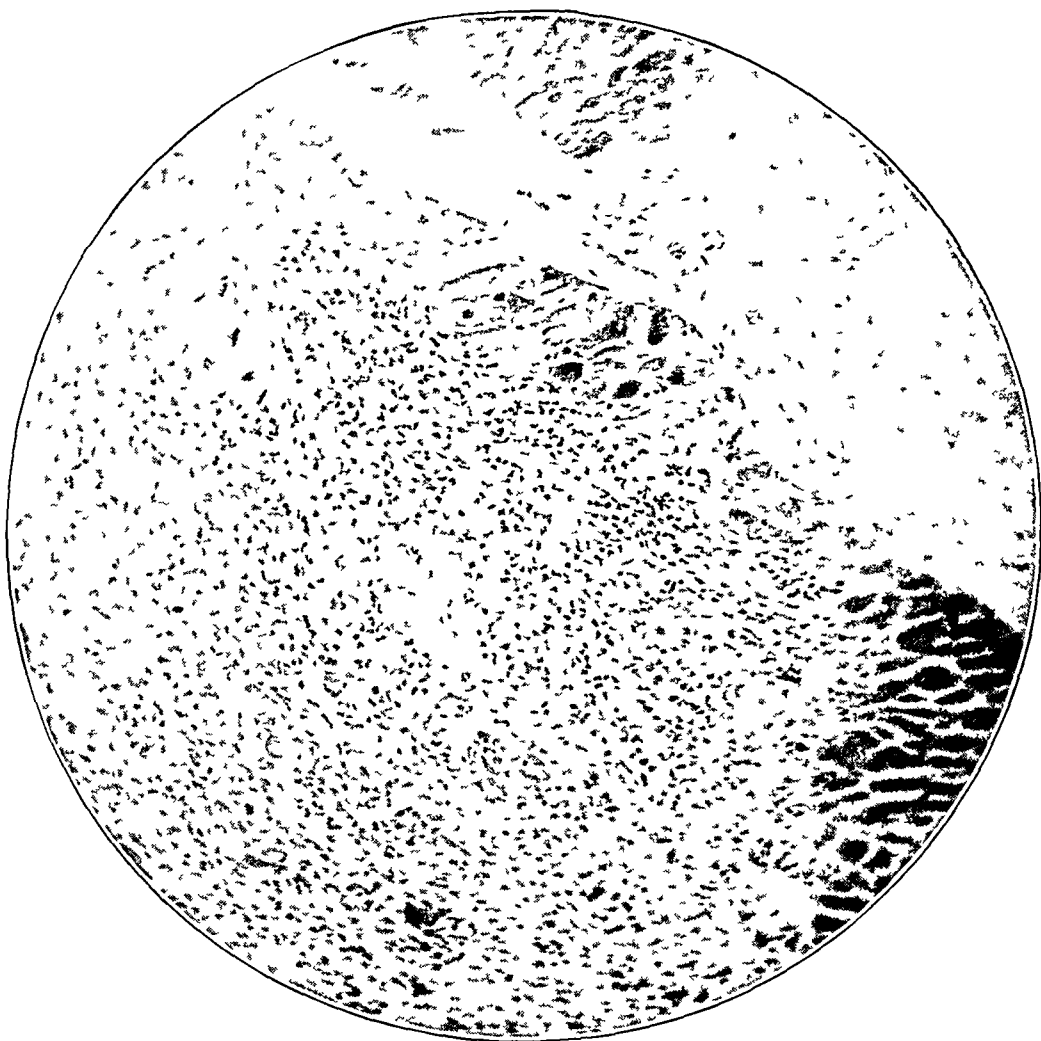


Fig 1—The lesion in the acute phase, showing the somewhat irregular shape, the sharp borders and the acute degeneration of the cytoplasm (low power)

largely monocytes, which made their appearance when the cytoplasm, although disintegrating, was still fairly abundant (fig 3). Polymorphonuclear cells and, more infrequently, some lymphocytes were occasionally found, but they did not constitute a prominent feature. As the cytoplasm was lost, and only the reticulum remained, the invading cells also were affected and likewise disappeared (fig 4). Fatty degeneration of the fibers in the lesion was conspicuous by its absence. Occasionally

a few fibers of the adjacent myocardium were affected, but in only 2 instances, both in the cardiac-sclerotic group, was there a generalized fatty myocardial change. In both of these cases syphilis was a complication. This myocardial lesion has been described previously in a case reported by Roesler and Soloff¹

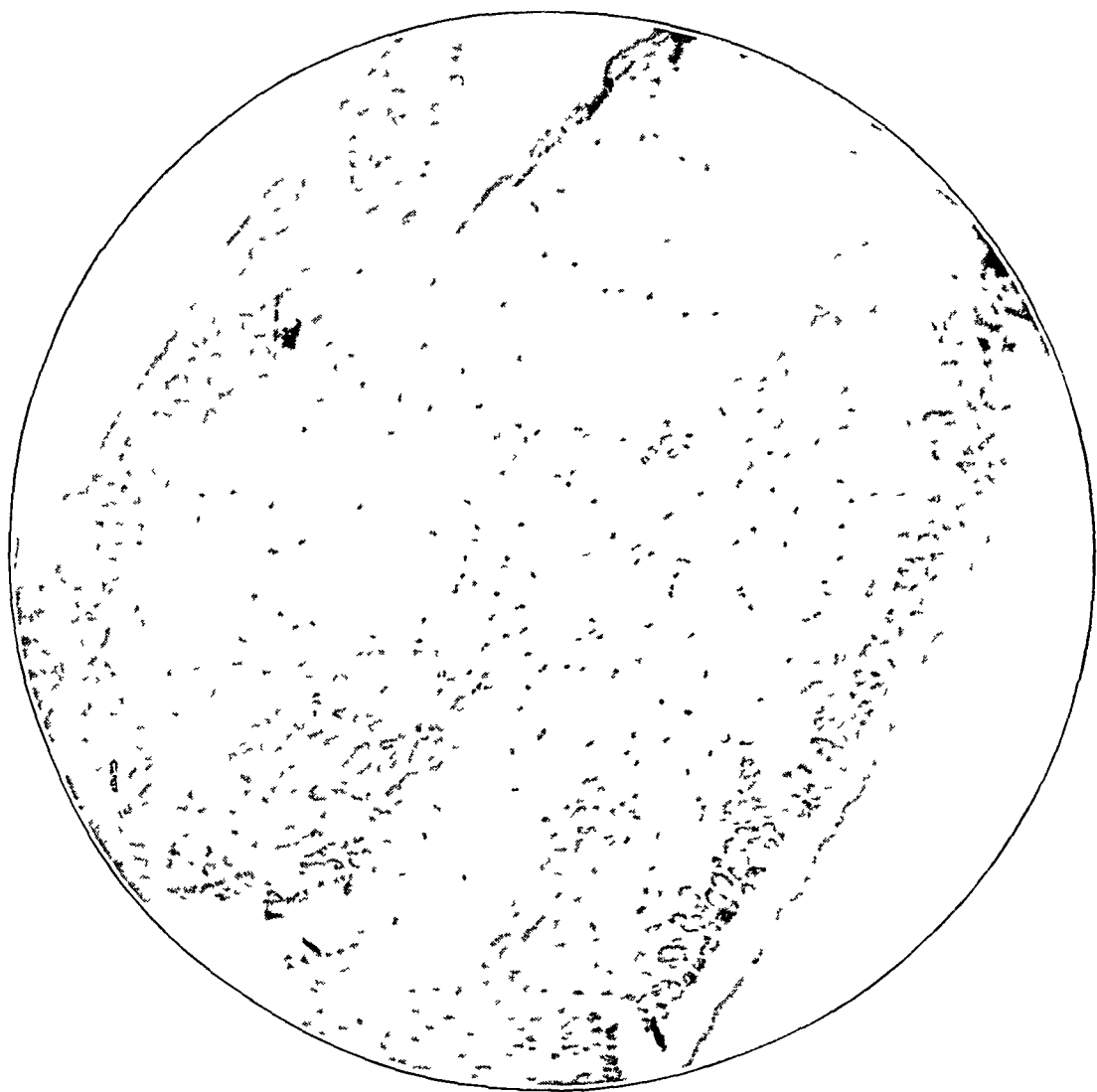


Fig 2—The fully developed lesion, showing only the remains of reticulum. This view also shows the location in the deep myocardium and the narrow preserved muscle beneath the endocardium (low power)

The myocardial branches of the coronary arteries were, as a whole, fairly normal. In the larger branches, however, sclerotic changes were not uncommon. Less frequent was medial hypertrophy, usually focal in distribution and never generalized. In 17 cases the small muscular

¹ Roesler, H, and Soloff, L. A. Report of a Case of Left Ventricular Failure with Unusual Anatomical Changes in the Myocardium, *Ann Int Med* 9:477, 1935

branches showed acute thrombi or emboli (figs 5 and 6), 8 of these cases were in the cardiac-sclerotic group (in 1 the source was bacterial), 2 were in the noncardiac sclerotic group, 4 were in the group in which acute coronary thrombosis was noted, and 3 were in the nonsclerotic group (in 1 the source was a primary bronchogenic carcinoma) These thrombi were present only in the walls affected by the miliary infarctions

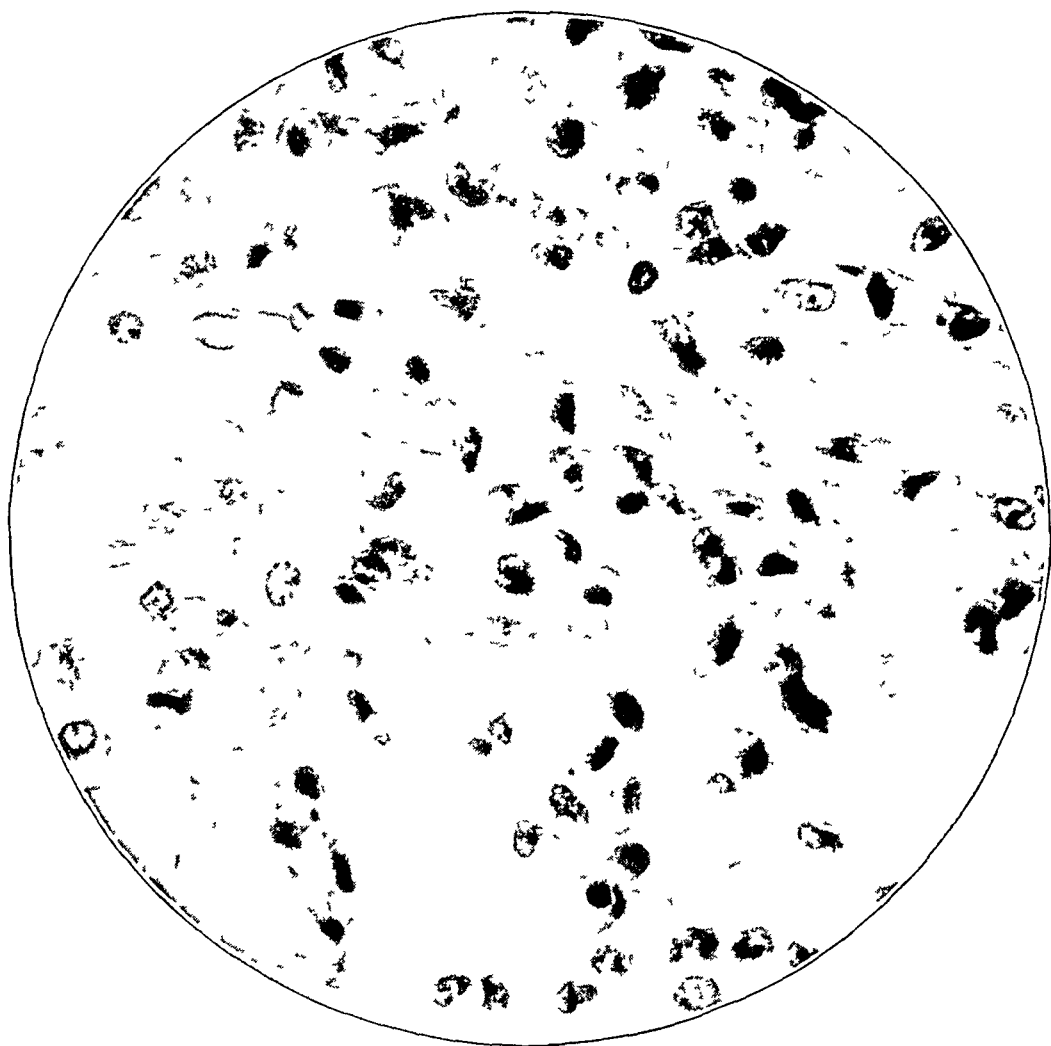


Fig 3—High power magnification of the section shown in figure 1 Note the swollen nuclei of the muscle and the remains of cytoplasm, lipochrome and reticulum

Grossly, the chief characteristics of the hearts in which the lesions were found were soft consistency, pale color and mottled appearance of the myocardium On transection of the ventricular walls, the pale brown myocardium had a speckled or mottled appearance from the presence of minute foci or streaks, light yellow, fawn colored, gray or gray-yellow In some hearts the lesions were larger, about the size of a nickel or a quarter, and had all the features of massive cardiac infarction

It was of interest to note the incidence of these larger lesions in the various groups. Of the 51 cases in the cardiac-sclerotic group, 7 showed the coarse acute infarctions. A fairly large lesion was found in 1 of the 15 cases in the noncardiac-sclerotic group, and among the 9 cases in the nonsclerotic group there were 2 in which macroscopic lesions were noted, one lesion comparatively small and the other massive.

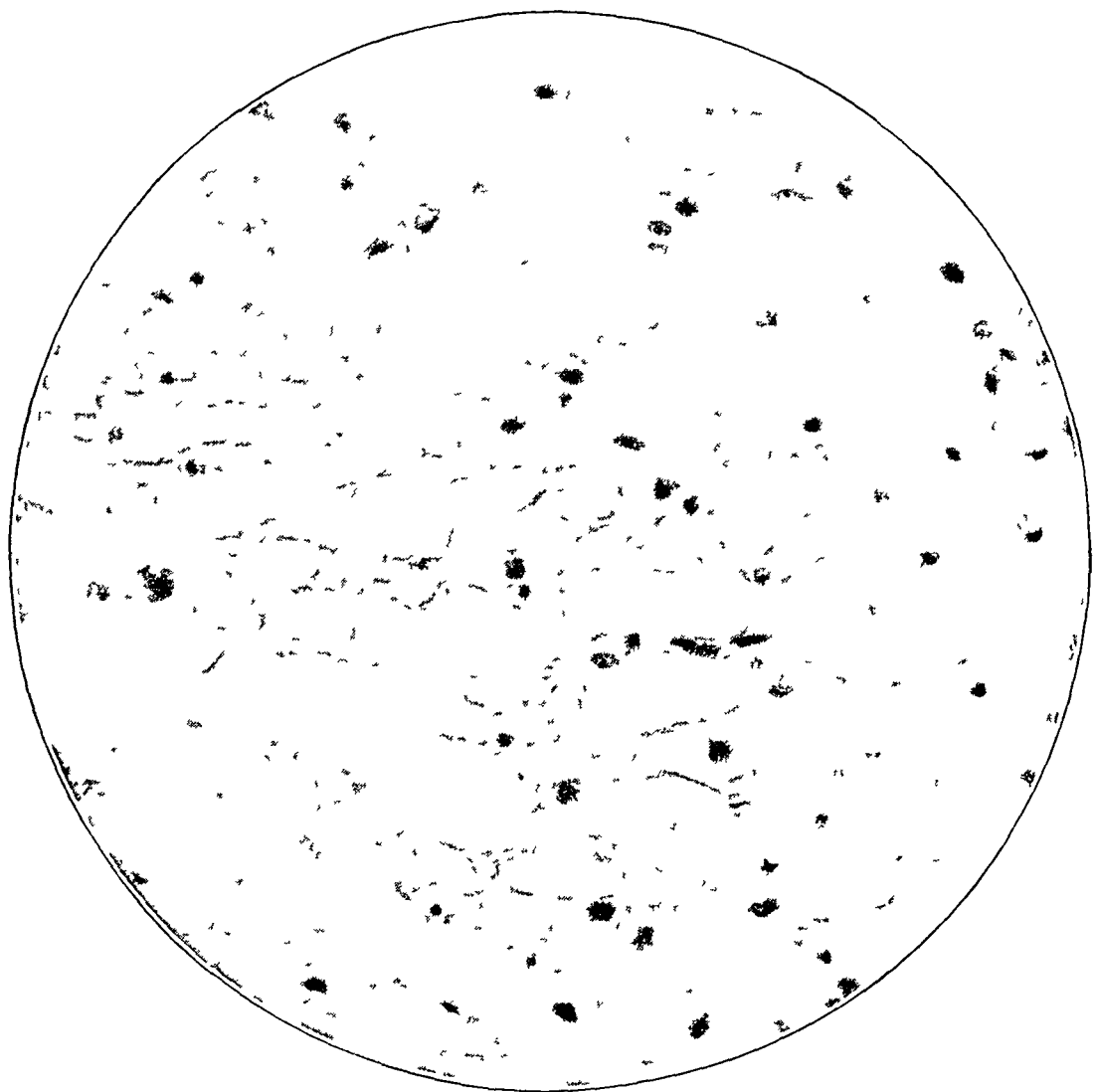


Fig. 4—High power magnification of the area shown in figure 2. Note the remains of the reticulum. There are still a few remnants of cytoplasm.

Thorough histologic examinations were carried out on the 24 hearts with recent coronary occlusion. Massive recent infarction was absent in 5. Grossly, the myocardium in these hearts showed the characteristics described previously (soft consistency, pale color and mottling), and microscopically there were extensive miliary infarcts. In the remaining 19 hearts, the myocardium beyond the area of massive infarction had similar gross and microscopic features.

Hypertrophy of the heart was frequent (table 2) As can be seen in this table, the weight of the heart in almost 75 per cent of the cases in the cardiac-sclerotic group was 600 Gm or more, and in only 1 case was the heart not hypertrophied In most of these cases the cardiac abnormality was associated with hypertension, the systolic blood pres-

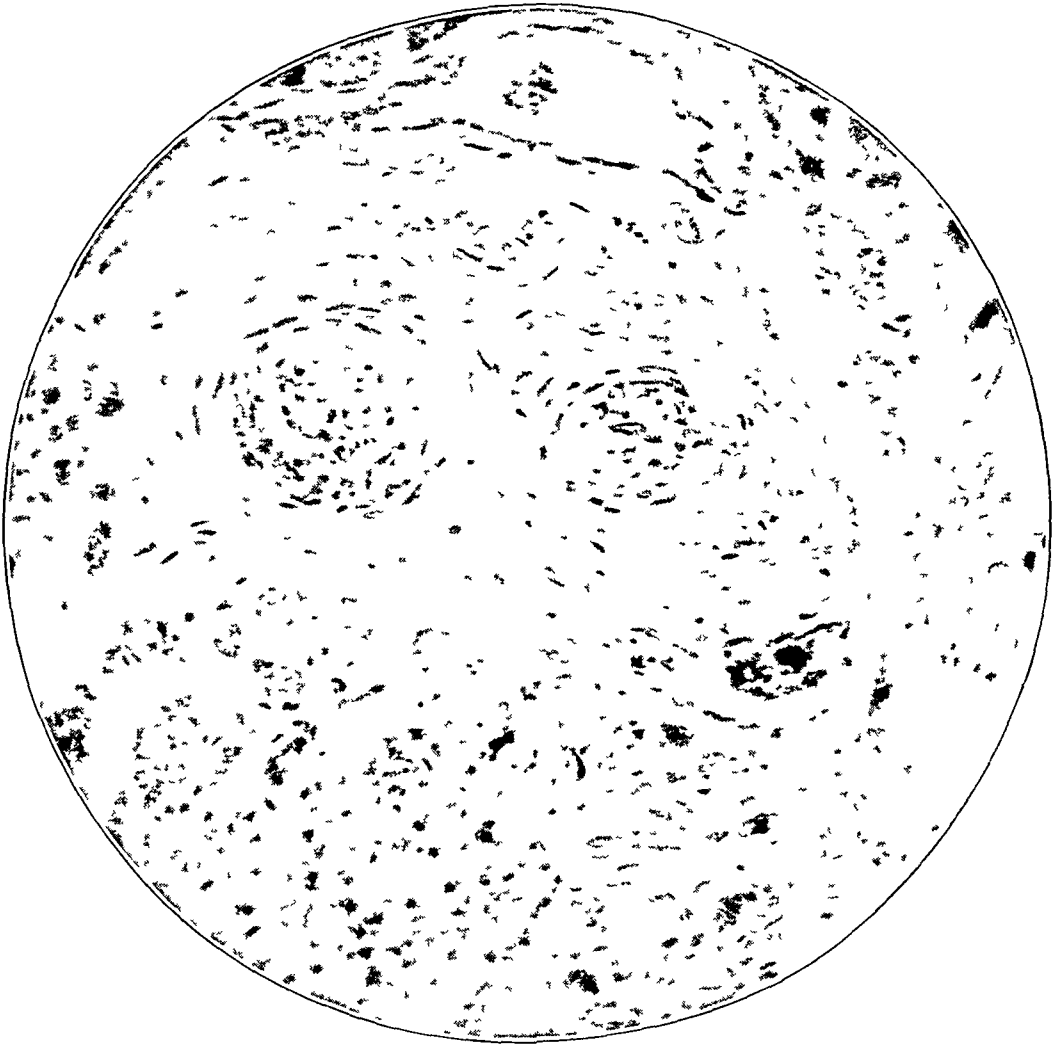


Fig 5—Acute thrombosis in a myocardial branch of a coronary artery Most of the small arteries were normal, as is shown

TABLE 2—Weights of Hearts in Various Groups

Group	Hearts with Given Weight, Gm						800 or More
	299 and Under	300-399	400-499	500-599	600-699	700-799	
Cardiac-sclerotic	0	1	6	6	21	11	6
Noncardiac sclerotic*	0	3	3	3	2	0	0
Acute coronary thrombosis†	0	9	10	13	6	9	2
Nonsclerotic‡	4	0	0	0	1	3	0

* No weight was recorded in 4 cases, in 1 case the heart was noted as enlarged

† No weight was recorded in 3 cases, all the hearts were enlarged 1 was very large

‡ No weight was recorded in 1 case, the heart was noted as small

sure varying from 155 to over 200 mm of mercury. Vascular changes of the type associated with essential hypertension were found in the kidneys in all but 5 instances. In the case in which the heart was small, the kidneys and the blood pressure were normal. In 1 case the enlarged heart was due to syphilitic aortic valvulitis with incompetency. In 3 cases there was no evident explanation for the hypertrophy. In

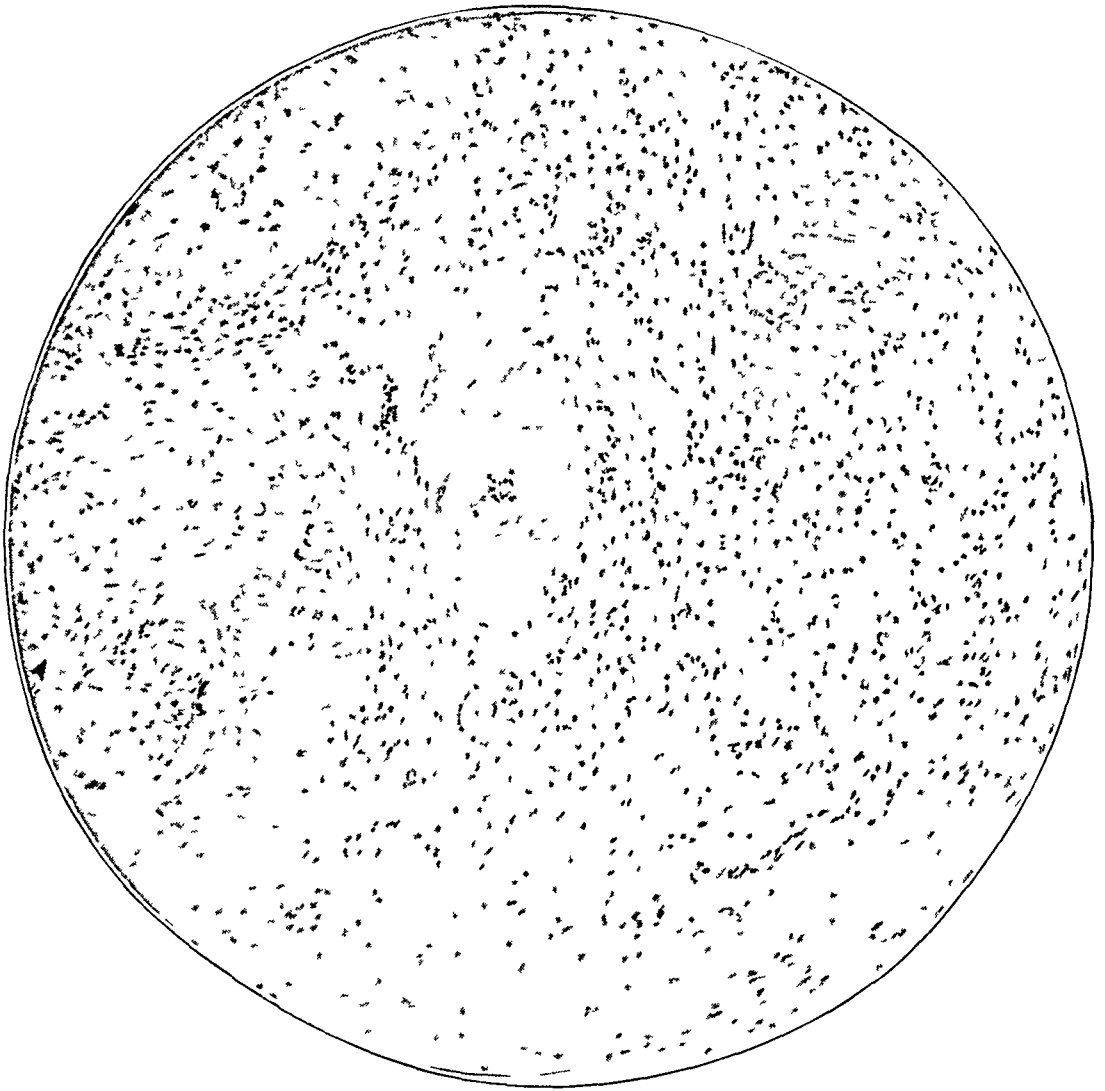


Fig 6—Acute thrombosis in some of the hyperplastic small vessels. The view also shows one small vessel free from thrombus.

the noncardiac-sclerotic group increase in the weight of the heart tended to be less marked, when noted, it was usually associated with essential hypertension, as in the other group. In the group of cases of acute coronary thrombosis the greatest extremes in weight were noted, but in general the hypertrophy was of the same hypertensive character. The nonsclerotic group was more heterogeneous. Half the hearts were small, half were very large. The basis of the hypertrophy was essential hypertension in 2 cases (complicated in 1 by chronic active rheumatic

valvulitis), syphilitic valvulitis with incompetence in 1 case, and stenosis of the aortic and mitral valves from healed rheumatic heart disease in 1 case

The distribution by race conformed to the generally accepted views of the incidence of coronary disease. In the cardiac-sclerotic group there were 39 white persons and 11 colored, in the noncardiac-sclerotic group 14 white persons and 1 colored, in the group with acute coronary thrombosis 43 white persons and 8 colored, and in the nonsclerotic group 7 white persons and 2 colored. There was 1 male Japanese in the first group, and there was 1 male Amerind in the third. The proportion of white to colored patients with acute coronary thrombosis was somewhat higher than that usually recorded, 5.4:1, in the cardiac-sclerotic group the proportion was 3.5:1. In the noncardiac-sclerotic group only 1 of the 15 patients was colored.

The distribution by sex also conformed to the usual views. Of the white persons in the cardiac-sclerotic group 28 were men and 11 were women, of the colored persons, 7 were men and 4 women. In the group with acute coronary thrombosis, of the white patients, 33 were men and 10 were women, of the colored patients, 7 were men and 1 was a woman. In the noncardiac-sclerotic group were 8 white men and 6 white women, the single colored patient was a Negress. In the nonsclerotic group the white women outnumbered the men 4:3, the 2 colored patients were a 10 year old girl and a man.

In most cases the patients were in the later periods of life, from the fourth decade on. The youngest patient, a child of 10 in the nonsclerotic group, and the oldest, a man of 75 with acute coronary thrombosis, were both Negroes. Certain relationships between age, race and sex were noted. Among the patients in the sclerotic-cardiac group, the youngest white man was 41, the youngest white woman was a decade older, 50. The oldest white man and the oldest woman were in the same decade of life, the eighth. Among the colored patients in this group the youngest man was 38 and the youngest woman, 39, both were thus younger than the youngest white patients. The ages of the oldest man and the oldest woman were about the same for the colored as for the white patients, 79 and 68. The findings were similar in the group with acute coronary thrombosis. Among the white patients, the youngest man was 43, the youngest woman, 55, the oldest man and the oldest woman were 92 and 80, respectively, a decade or two older than the oldest of the first group. Similar extremes of age (52 and 95) were found among the colored men. There was only 1 Negro woman, 53. Among the white patients in the noncardiac-sclerotic group there was a reversal of the youngest ages for men and for women. The youngest woman was 40 and the youngest man, 54. The oldest man and the

oldest woman were both 75. The significance of the reversal of the lower limit of age in reference to sex in this group is doubtful. A much larger series might show the usual finding—the women a decade older than the men. The only colored patient in the group was a Negress of 42. The patients in the nonsclerotic group, with the exception of the child mentioned before, were all in the sixth and seventh decades.

The clinical syndrome presented during the terminal phase in the great majority of the cases of all the groups was that of sudden left ventricular failure. The characteristic symptoms, either singly or in various combinations, were sudden extreme dyspnea, profuse perspiration, extreme weakness, marked tachycardia, a pulse of poor quality and apprehension. Cyanosis was common, sometimes it was extreme, and occasionally it was absent. It was of interest to note that when cyanosis was absent and death was not delayed more than a few hours the acute miliary lesions were strictly limited to the left side of the heart. Anginal pain was rarely present during the final attack.

Death was seldom delayed for more than four days. Usually it occurred within twenty-four or forty-eight hours of the cardiac collapse. Sudden death was common. Among patients in the cardiac-sclerotic group it occurred 11 times, among those in the noncardiac-sclerotic group, 4 times, among those with acute coronary thrombosis, 15 times, among those in the nonsclerotic group, 3 times. In the last group the hearts of 2 patients were greatly hypertrophied. Although anginal attacks had occurred previous to death in very many of the cases, sudden death occurred in 5 patients in the cardiac-sclerotic group and in 1 patient in the group with acute coronary thrombosis who had no attack of angina and in whom cardiac failure had been of a congestive nature. Four patients of the noncardiac-sclerotic group and 3 in the group with acute thrombosis had no history of previous cardiac disability.

From the histories, the attacks of cardiac dysfunction that occurred prior to death were usually of the type recognized as characteristic of coronary sclerosis. Anginal pain or its equivalent had been experienced for varying lengths of time previous to the final episode. In the cardiac-sclerotic group such pain occurred in 36 of 49 cases, in the group in which acute coronary thrombosis was present, in 27 of 42, in the nonsclerotic group, in 3 of 8. It occurred in only 1 case in the noncardiac-sclerotic group, in this instance a single attack of pain was experienced four months prior to death. In the 3 cases in the nonsclerotic group the heart was hypertrophied. In the remaining cases the data were insufficient to establish the previous history, usually because the patient's statements were unreliable or because death occurred soon after admission to the hospital.

Although it is not of primary interest in this paper, it seems worth noting that many hearts showed evidence of good healing in lesions that seemingly were of the character of miliary infarctions. These healing lesions may possibly explain the previous acute episodes from which the patients had recovered.

Of the possible etiologic factors, there is, first, arteriosclerosis of the coronary arteries. Throughout the entire series of cases there was no uniformity in the condition of the superficial coronary arteries. In the nonsclerotic group, they were normal. Marked degrees of sclerosis were present in about half of the cases (9) in the noncardiac-sclerotic group, in about two thirds of the cases (35) in the cardiac-sclerotic group and in almost all of the cases (50) in the group in which acute thrombosis was noted. Except for the last group, in which the lumens of the coronary arteries tended to be narrowed, it was noted that with marked changes of the coronary walls, the lumens were as frequently wide as narrow. Old thromboses were noted with a frequency about parallel to the degree of arteriosclerosis: in 2 cases in the noncardiac group, in 9 in the cardiac-sclerotic group and in 14 in the group of cases in which recent thrombosis was present. The wide variation, then, of the condition of the coronary arteries militates against arteriosclerosis being in itself the precipitating factor in acute miliary infarctions.

Syphilis of the aorta was found 14 times in the entire series. A history of syphilis was given in 1 case, but its presence could not be demonstrated at autopsy. Involvement of the arch of the aorta or of the commissures, resulting neither in valvular deformity nor in stenosis of the mouths of the coronary arteries, was present in 8 cases. The syphilis in these cases seems an incidental finding, unrelated to the acute myocardial lesion, since in all cases the more severe degrees of arteriosclerosis were present. Isolated atresia of the mouth of one or of both coronary arteries was present in 3 cases. In 1 of these atresia of the mouth of the right coronary artery was associated with acute thrombosis of the anterior descending artery. In a second case atresia of both mouths, with acute thrombosis of the right coronary artery, was complicated by chronic active rheumatic valvulitis and superimposed acute endocarditis. The third case, in which there was atresia of both mouths, was complicated, as were the other 2, by marked arteriosclerosis. The complicating factors rendered it unlikely that syphilis was the sole agent causing the miliary infarctions, although the combination may be of some significance.

An incompetent aortic valve was present in 3 cases. In the first, in the cardiac-sclerotic group, there was atresia of the mouth of the right coronary artery, the miliary infarctions were in the left ventricle and

interventricular wall in the areas supplied by the left coronary artery. In the second case, in which, likewise, the mouth of the right coronary artery was affected, there were acute thromboses of the left circumflex and anterior descending arteries. In the third case, in the nonsclerotic group, a massive acute infarction was present. This, then, remains the single instance in which syphilis seems to have played a definite role. On the whole, however, it seems justifiable to state that syphilis plays a minor role in the entire group.

Lesions of rheumatic heart disease were found in 8 cases—1 in the cardiac-sclerotic group, 3 in the noncardiac-sclerotic group, 2 in the group in which acute thrombosis was present and 2 in the nonsclerotic group. In 1 case each of the first and third groups, the lesions were chronically active. The others were healed. In all cases, stenosis of the mitral valve or of the mitral and aortic valves was present. That rheumatic disease as such has any bearing on the production of miliary infarction seems very doubtful, to the best of our knowledge, the lesion has never been described in reports of cases of active rheumatic carditis, nor have we seen it in such cases in this laboratory. However, rheumatic disease may have some bearing because it may produce a stenotic aortic lesion which in itself is known to render a heart susceptible to any damage.

Roesler and Soloff were of the opinion that in their case a toxic element arising from acute pneumonia was the causative factor underlying the acute myocardial lesion. In this series, also, infection was present in a large majority of the cases. Bacteria were never demonstrated within the lesion itself in any instance. In a case previously reported,² thrombosis of a main coronary artery was precipitated by gram-positive cocci, enmeshed in fibrin, originating in acute lobar pneumonia.

Of the 17 cases in which there was acute thrombosis or embolism of the intramuscular branches of the coronary arteries, bacteria were demonstrable in 1 case, they probably arose from a chronic infection of the lower genitourinary tract. Of the remaining 16 cases, an acute infectious process was present in 11. In 1 case in the nonsclerotic group the heart was hypertrophied as a result of chronic active rheumatic valvulitis and essential hypertension, and acute endocarditis of the mitral valve and acute bronchopneumonia were present.

There were 2 instances of infection in the noncardiac-sclerotic group. In 1 case, after cholecystectomy, a nonhemolytic streptococcus was isolated, cellulitis developed at the site of incision and bronchopneumonia ensued. Death was sudden. In the second case an obstruction-infection

² Lisa, J. R. Unusual Findings in a Case of Acute Coronary Thrombosis, *Arch. Path.* 23:449 (March) 1937, *Proc. New York Path. Soc.*, 1936-1937, p. 3.

syndrome developed after prostatectomy, the patient died suddenly after having had one anginal attack a few days previously

In 2 of the cases in which acute coronary thrombosis was a feature an acute pneumonic process was noted. In 1 of these there were anginal symptoms, and a genitourinary obstruction-infection syndrome developed as a result of urethral stricture. In the other case lobar pneumonia was present, and the signs and symptoms were primarily pulmonic.

There were 4 instances of bronchopneumonia and 2 of lobar pneumonia in the cardiac-sclerotic group. The cases of lobar pneumonia were of special interest. A Negro woman of 39, who had suffered from congestive heart failure and angina for ten months, had a terminal illness of two days' duration, with severe congestive heart failure and signs of pulmonic consolidation. The pneumonia was in the gray stage at death, it was evidently several days older than the history indicated. In the second case the patient was a white man of 72 who had had sudden severe congestive heart failure for only three weeks before death.

The 82 cases in which thrombi were not found are still to be considered. This number includes 20 of the 24 cases in which acute coronary thrombosis was present in which thorough histologic studies were carried out.

In the nonsclerotic group there were 2 cases in which acute infection was present. The 10 year old Negro girl had generalized miliary tuberculosis, a white woman with Hodgkin's disease had bilateral suppurative maxillary gland infection and bronchopneumonia. Acute infection was present in 9 cases in the noncardiac-sclerotic group. In 4 cases there were acute cerebrovascular accidents and bronchopneumonia. In 1 case there was chronic pulmonary tuberculosis and acute coccial bronchopneumonia. In 1 case there was prostatic hypertrophy with an obstruction-infection syndrome, and the blood culture was positive for *Bacillus proteus*. In another, general peritonitis developed following rupture of a senile uterus in which septic endometritis was present secondary to stenosis of the external os. In another case, after an amputation for diabetic gangrene, there was a septic course for four days. In the last case there was uremic coma with bronchopneumonia.

In 9 of the cases in which acute coronary thrombosis was noted there were infections. In 1 case there were massive cerebral hemorrhage, acute lobar pneumonia and acute suppurative nephritis, gram-positive cocci were found in sections of the kidney. In 6 cases there was acute bronchopneumonia, once with empyema, once with embolic glomerulitis and once with acute miliary myocardial abscesses. In another case there was a carbuncle of the back, and in the sixth case there was acute endocarditis and the blood culture was positive for *Streptococcus haemolyticus*. Acute infection was present in 22 instances in the

cardiac-sclerotic group In most of them the infection was acute bronchopneumonia, although each of the following conditions was found once cellulitis of the leg, carbuncle, acute pulmonary tuberculosis and infection of the lower genitourinary tract In 3 cases pneumonia was complicated by empyema, in 1, by pericarditis It was of interest to note that the temperature seldom was a good indication of infection In many cases, even when extensive inflammation was present, the temperature was never above 100 F, the clinical syndrome was cardiac

Chronic infections were present in 19 of the remaining 40 cases 1 in the nonsclerotic group, 3 in the noncardiac-sclerotic group, 4 in the group in which coronary thrombosis was recorded, and 11 in the cardiac-sclerotic group In most of these the infection was chronic tubular bronchiectasis, although pelvic infection and chronic tuberculosis were also found It should be stated in passing that in many cases acute bronchopneumonia followed chronic bronchitis of the same type Two factors were noted which might have been the basis for increased susceptibility to the toxic effect of infection in this group of cases With three exceptions, in all cases there was extreme cardiac hypertrophy, and in most of them, severe arteriosclerosis In almost half of the cases there were old canalized thrombi in the superficial coronary arteries

Infection was not demonstrated in the remaining 26 cases, there was a suggestive finding in 1 case only, this was in a case in the nonsclerotic group in which sudden death occurred in the convalescent period after pneumonia Of the entire series, however, infection was demonstrable in practically 75 per cent of the cases

If infection, particularly pneumonia, is a causative factor in precipitating acute miliary infarctions, the occurrence of the latter should correspond closely to the winter months In this series, 65 instances of miliary infarction occurred in the period from November to April, and 34 in that from May to October In the latter group, active infections were present in 58 per cent of the cases It is of interest to note also that most of the cases in which chronic purulent bronchiectasis was unassociated with acute bronchopneumonia were included in the winter group

SUMMARY AND CONCLUSIONS

An acute lesion of the myocardium called miliary infarction is reported It was found in 99 cases and was usually associated with the clinical syndrome of sudden left ventricular failure The material reviewed consisted of 2,857 cases in which autopsy was performed, it was divided into two main groups (1) cases in which coronary arteriosclerosis was present and (2) cases in which this condition was not present The first group was subdivided into a cardiac-sclerotic group

and a noncardiac-sclerotic group on the basis of clinical symptomatology. The lesion was most frequent in the cardiac-sclerotic group, much less so in the noncardiac-sclerotic group and least frequent in the non-sclerotic group. In the cardiac-sclerotic group its incidence was equal to that of acute coronary thrombosis. The greatly hypertrophied heart with marked sclerosis of the coronary arteries seemed the most susceptible to the occurrence of the lesion.

In 17 of the 99 cases, thrombi or emboli of the myocardial branches of the coronary arteries were found. The thrombosis was bacterial in 1 instance and malignant in another. In 1 case thrombosis of a main coronary artery was caused by a bacterial embolus arising from acute lobar pneumonia. An infectious nature of the myocardial lesion itself was never demonstrated. Infections in other organs, most frequently the lungs, were present in the majority of cases.

It is our opinion that the lesion in the majority of cases is toxic in nature and in a small percentage is due to embolism or thrombosis of the muscular branches of the coronary arteries, usually, even in this group, associated with infection.

SULFANILAMIDE IN TREATMENT OF INFECTIONS OF THE URINARY TRACT DUE TO BACILLUS COLI

LOWELL A RANTZ, M D
AND
CHESTER S KEEFER, M D
BOSTON

It is common knowledge that once the colon bacillus leaves its normal habitat it sets up inflammation and causes acute or chronic disease in different organs. The two most frequent locations for such disease are the biliary and the urinary tract. In the urinary tract the colon bacillus finds an environment that is favorable for its growth. It would appear that the factors which permit the survival and growth of the colon bacillus in the urinary tract are (1) conditions which cause stasis of the urine and (2) the chemical composition and reaction of the urine.

In the treatment of such infections of the urinary tract two methods are in general use: (1) those which relieve conditions that favor stasis of urine and (2) those which change the reaction and chemical composition of the urine so that the organisms have difficulty in surviving.

To relieve stasis, obstructions to the free flow of urine are removed or relieved. To change the reaction and chemical composition of the urine, methods that make the urine more acid or cause the urinary excretion of chemicals which have an unfavorable effect on the growth of the colon bacillus are in common use.

One of the chemotherapeutic agents that have had wide use within the past three years in the treatment of infections of the urinary tract is sulfanilamide. Imhauser and Huber¹ were among the first to call attention to its possible value, and with the appearance of the report by Kenny and his co-workers² its use was placed on a rational footing. They studied 46 cases of acute pyelitis and found that the urine was easily sterilized in all cases when moderate doses of the drug were given by

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1 (a) Imhauser, K. Ueber die Behandlung septischer Erkrankungen mit Prontosil, *Med Klin* **31** 282, 1935. (b) Huber, H. G. Ueber Prontosil bei der Behandlung der kindlichen Pyurie, *Munchen med Wchnschr* **83** 2014, 1936.

2 Kenny, M., Johnston, F. D., von Haebler, T., and Miles, A. A. P-Amino Benzene Sulphonamide in Treatment of Bacterium Coli Infections of the Urinary Tract, with a Note on the Two-Plate Bacterial Count, *Lancet* **2** 119, 1937.

mouth The etiologic agent in all of their cases was the colon bacillus In vitro studies with the organisms from these patients revealed that there were marked variations in the sensitivities of different strains to the drug, and that both bacteriostatic and bactericidal effects were demonstrable in varying degree No correlation was demonstrable between the ease of producing clinical sterilization of the urine and the resistance of the homologous organism to sulfanilamide in vitro

Since that time many articles have appeared on the subject, the most noteworthy being those of Helmholz,³ who described the marked bactericidal effects of the drug in vitro on all the bacteria commonly found as causative agents in infections of the urinary tract, including *Escherichia coli*, *Bacillus proteus*, *Aerobacter aerogenes*, staphylococci and all streptococci except *Streptococcus faecalis* Helmholz also postulated that the bactericidal effect noted in vitro was greatly enhanced in an alkaline urine (p_H 6.5 or greater)

The majority of the other reports⁴ have discussed the use of sulfanilamide in the treatment of infections of the urinary passages associated with obstructions or other gross abnormalities of these organs, of the type usually seen in urologic or surgical wards For this reason we began a study of the acute infections of the urinary tract so frequently seen in the medical wards This paper presents the clinical data for 17 cases of patients with infections of the urinary tract and the bacteriologic studies made in vitro on organisms isolated from the urine of these patients

The diagnosis of pyelonephritis was made in those cases in which chills, fever and pain in the flanks, with or without dysuria and frequency, were the prominent clinical features When dysuria and frequency occurred with only minimal evidence of disease in the upper part of the urinary tract, the condition was interpreted as a local cystitis In both diseases, bacteriuria and pyuria were marked and the colon bacillus was initially isolated in pure cultures Hypertension and albuminuria were absent and the eyegrounds were normal in every case The excretion of casts was normal, an abnormal number of red blood cells was found in the urine only in those instances in which the symptoms of cystitis were present

3 Helmholz, H F Bactericidal Power of Urine After Administration of Prontylin by Mouth, Proc Staff Meet, Mayo Clin **12** 244, 1937 Helmholz, H F, and Osterberg, A E Rate of Excretion and Bactericidal Power of Sulfanilamide (Prontylin) in Urine, *ibid* **12** 377, 1937

4 Vest, S A, Hill, J H, and Colston, J A C Experimental and Clinical Observations on Sulfanilamide in Urinary Tract Infections, J Urol **41** 31, 1939 Buchtel, H A, and Cook, E N The Use of Sulfanilamide in Treatment of Urinary Infections, Proc Staff Meet, Mayo Clin **12** 444, 1938 King, K B Treatment of Urinary Infections with Particular Reference to Sulfanilamide, Internat Clin **3** 208, 1938 Young, H H, and Vest, S A Treatment of Hematogenous Nephritis with Sulfanilamide, Ann Surg **108** 828, 1938

All specimens of urine from women were collected by sterile catheterization, the infecting organism was isolated on eosin methylene blue and blood agar plates, and the number of organisms was estimated by appropriate serial dilution, 1 cc of each dilution being poured in plain agar plates. Sulfanilamide in blood and urine was estimated by the method described by Marshall⁵. The excretion of formed elements in the urine was estimated in a selected group by the method described by Addis,⁶ in certain instances timed and concentrated, and in others timed but unconcentrated, specimens of the urine being used. The sedimentation rate was measured by the method of Rourke and Ernstene⁷ by which the values are expressed in millimeters of settling during the period of most rapid fall.

ANALYSIS OF CASES

The data from 14 of the 17 cases are summarized in table 1. The other 3 cases will be discussed in greater detail because they present many interesting features which require emphasis.

The cases were divided into four groups on the basis of underlying or predisposing processes. It will be demonstrated that the effectiveness of the drug, as judged by its ability to sterilize the urine and assist in eventual cure, varies in each group.

Group 1 Infection of the Urinary Tract Associated with Pregnancy—The data for cases 1 to 4 in table 1 summarize the pertinent facts in the cases of 4 young women in whom severe to moderately severe acute pyelonephritis developed in the second or third trimester of an otherwise uneventful pregnancy. In the first 3 cases the temperature had returned to normal and most of the symptoms had subsided on a regimen of rest and administration of large volumes of fluid, but bacilluria and pyuria were persisting, when the drug was first administered. Treatment with sulfanilamide was followed by permanent sterilization and clearing of the urine in 2 cases. In the third the medication was irregular and the concentration of sulfanilamide in the blood and urine was low. While marked reduction was noted in the total number of organisms excreted, they never completely disappeared, and the patient was discharged from the hospital free of symptoms but with persistent bacilluria.

Case 4 is of great interest, the clinical course is shown in chart 1. The patient was admitted with symptoms and signs of pyelonephritis.

5 Marshall, E. K., and Litchfield, J. T., Jr. The Determination of Sulfanilamide, *Science* 88: 85, 1938.

6 Addis, T. Formed Elements in the Urinary Sediment of Normal Individuals, *J. Clin. Investigation* 2: 409, 1926.

7 Rourke, M. D., and Ernstene, A. C. A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, *J. Clin. Investigation* 8: 545, 1930.

which were so severe that the diagnosis of a complicating perinephric abscess was entertained. She was acutely ill, and the urine contained many bacilli and leukocytes. After the infection had continued to remain active for a period of one month in spite of the usual methods of treat-

TABLE 1—Data on Fourteen

Case	Age	Sex	Duration of Dis- ease at Beginning of Treat- ment, Days	Daily Dose of Sulfanil- amide, Gm	Duration of Treatment Days			Maximum Unacetylated Sulfanilamide, Mg per 100 Cc		pH	Urine	
					Total	First Sterile Urine Observed	After Sterila- zation of Urine	Urine	Blood		No. of B. coli per Cc	
											Before Treat- ment	After Treat- ment
1	33	F	12	3	12	3	8			5.9	95 000 000	0
2	25	F	20	2	8	3	5	50.0	4.1	6.0	125 000 000	0
3	18	F	15	2	9		0	23.0	2.5	6.8	200 000	6,000
4	27	F	38	4	5	4	1	50.0			120 000 000	0
5	19	F	4	4	10	3	7	65.0	3.4		90,000,000	0
			15	3	5	6	0	70.0	7.3	6.4	35,000 000	0
6	28	F	45	2	19	12	7	57.5	4.3	6.5	170,000	0
7	31	F	7	8	6	3	3				1,000 000+	0
8	40	M	18	3	17	0					Very many	
9	26	M	45	4.6	17	5	12	93.0	3.8	6.5	50 000,000	0
			67	5	20		0	139.0	6.7	6.2	1,000*	1,000*
			4	5	10	10	0	42.4	9.6	6.4	1 000 000+	0
10	60	F	365+	2	16		0	41.0	9.5	5.7	125,000,000	43,000
11	50	F	360+	3	13		0	70.0	7.5	7.2	1,000 000	1 000
12	30	F	14	3	5		0	44.0	8.5	5.7	30,000 000	1 200
13	35	F	21+	3	5	5	0	100.0	10.0	7.0	125 000,000	0
14	27	M	22	4	8		0	63.8	6.1		50 000	0
15	31	M	7	4	9		0				Innumerable	0†
			11	5.0	13			92.0	8.7	6.6	19 000 000	160 000
			33	5.0	4			45.0			10,000 000	23,000
16	53	F	102	3	34	1	33	82.9	6.3		1 850 000	0
			30+	8	7			68.0	7.2	6.5	106 000,000	1 000
17	23	F	40	6	5			32.2			10 000 000	
			28	3	9	2	7	101.0	5.0	6.0	1,000 000	0
			43	3	21	3	18	78.4	4.0	7.4	3,000 000	0
			4	8	15	6	9	363.0	13.7	7.0	40,000 000	0

* *Staphylococcus albus*

† After mandelate therapy

ment, sulfanilamide was exhibited by mouth. Within three days the urine was sterile, the patient felt well, and the medication was stopped. Bacteriologic and clinical relapse occurred after five days, but the symptoms were again relieved by the administration of the drug. Four months later she was well. She had no further symptoms referable to

the urinary tract and the renal function was normal. An uneventful labor had taken place in the interval.

From these cases, one can say that 2 to 3 Gm of sulfanilamide, given in divided doses over a twenty-four hour period, were adequate to effect

of the Seventeen Cases

Clinical Diagnosis	Complicating Factors	Retrograde Pyelograms	Follow Up	
			Days	Results
Very severe acute pyelo nephritis	Pregnancy, 5 mo, acute bronchitis	None	30	Urine sterile well
Moderately severe acute pyelonephritis	Pregnancy, 5 mo	None	360	Urine sterile
Moderately severe acute pyelonephritis	Pregnancy, 8 mo	None	6	10,000,000 B coli per cc urine
Severe acute pyelonephritis	Pregnancy, 7 mo	Normal	4	Recurrence
Recurrence			140	Well urine sterile
Mild acute pyelonephritis, cystitis	Acute bronchitis	None	30	Urine sterile
Very severe pyelonephritis, cystitis	Severe acute bronchitis	None	180	Well urine sterile
Very severe acute pyelo nephritis	None	Slight dilatation minor calyces	45	Well urine sterile
Severe acute pyelonephritis and cystitis	Moderate chronic prostatitis	Normal	10	Cystitis, severe
Severe cystitis, a relapse			5	Cystitis, mild
Mild cystitis a relapse			None	
Very severe acute pyelo nephritis	Hypospadias	Right pelvis dilated, left kidney rotated	7	Well, urine sterile
Cystitis	Hodgkin's disease chronic pyelonephritis?	Normal	None	
Cystitis	Diabetes mellitus chronic cystitis	Normal	350	Well 100,000 B coli per cc urine
Severe acute pyelonephritis	Acute tracheitis chronic cystitis	Normal	None	
Severe acute pyelonephritis	Chronic pyelonephritis rheumatic heart disease with decompensation	Slight dilatation right pelvis	180	Many B coli in urine
Moderately severe acute pyelonephritis	Chronic pyelonephritis	Slight dilatation pelvis	14	Recurrence
Acute pyelonephritis, a relapse			90	Well urine sterile
Severe acute pyelonephritis B coli septicemia	None	Double renal pelvis, left	500	Well 2 attacks of cystitis and 1 of perineal pain with fever since discharge
Very severe acute pyelo nephritis	None	Right superior calyx markedly narrowed and irregular	Died	
Acute pyelonephritis	Chronic pyelonephritis	Right pelvis dilated ureter kinked	3	Bacilluria recurred
Recurrence			4	Bacilluria recurred
Recurrence			365	Bacilluria present chronically ill

sterilization of the urine in 3 cases of pyelonephritis of pregnancy. In 1, its exhibition was twice associated with a disappearance of the fever and with clinical improvement. In the fourth case the treatment was inadequate, but the total excretion of organisms was reduced without sterilizing the urine. In all of the cases there were no further symptoms.

refeirable to the urinary tract after discharge from the hospital, and the pregnancy terminated normally in each case This study serves to emphasize the fact that the drug should be continued until all symptoms and signs of pyelonephritis have disappeared It should be added that the sterilization of the urine occurred without any preliminary alterations in the reaction of the urine and that the best results were obtained when the concentration of sulfanilamide in the urine was 50 to 100 mg per hundred cubic centimeters

Group 2 Pyelonephritis with No History of Previous Infection of the Urinary Tract—In this group there were 6 cases—cases 5 to 8 in table 1 and 2 others which will be considered later Cases 5 and 6 were those of patients with moderately severe to severe acute infections of the

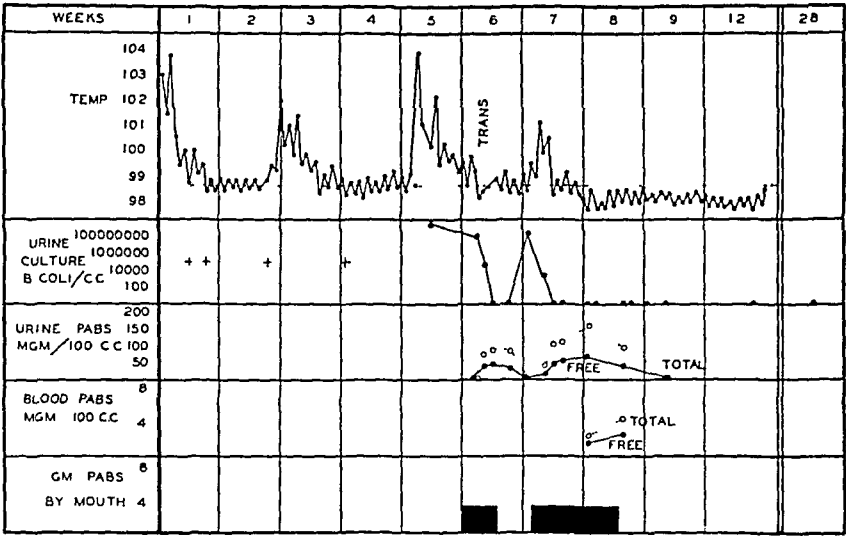


Chart 1—Course of events in case 4 In this and in succeeding charts, PABS indicates sulfanilamide

kidney whose clinical cure had been obtained by rest in bed and induction of an increase in the output of urine Sulfanilamide was given to these patients in an attempt to eradicate the bacilluria and pyuria which persisted after the signs of acute infection had disappeared In both cases the urine was sterilized within three and twelve days, respectively When the patients were reexamined after one and six months, respectively, they were well and the urine was sterile

Case 7 was that of a young woman who suffered from a very severe, prostrating infection Sulfanilamide was administered at the height of the disease, its administration was followed by disappearance of the symptoms and signs of infection and by sterilization of the urine within three days The patient had a severe reaction, with headache and nausea, so that clinical improvement was delayed until the withdrawal and elimination of the drug Once the latter was accomplished, she promptly became well, and had continued so when seen one month later

Case 8, which was similar to case 7, was that of a man in whom dramatic clinical improvement, with clearing of the urine, took place after the administration of sulfanilamide, all symptoms recurred after the withdrawal of the drug and again subsided on its administration. A mild cystitis, associated with the appearance of *Staphylococcus albus* in the urine, failed to respond to a third course, although a high concentration of the drug was obtained in the urine and blood. A progressive, slowly developing anemia had prompted the termination of the first course but did not recur on subsequent occasions when the drug was given in large doses for a prolonged period.

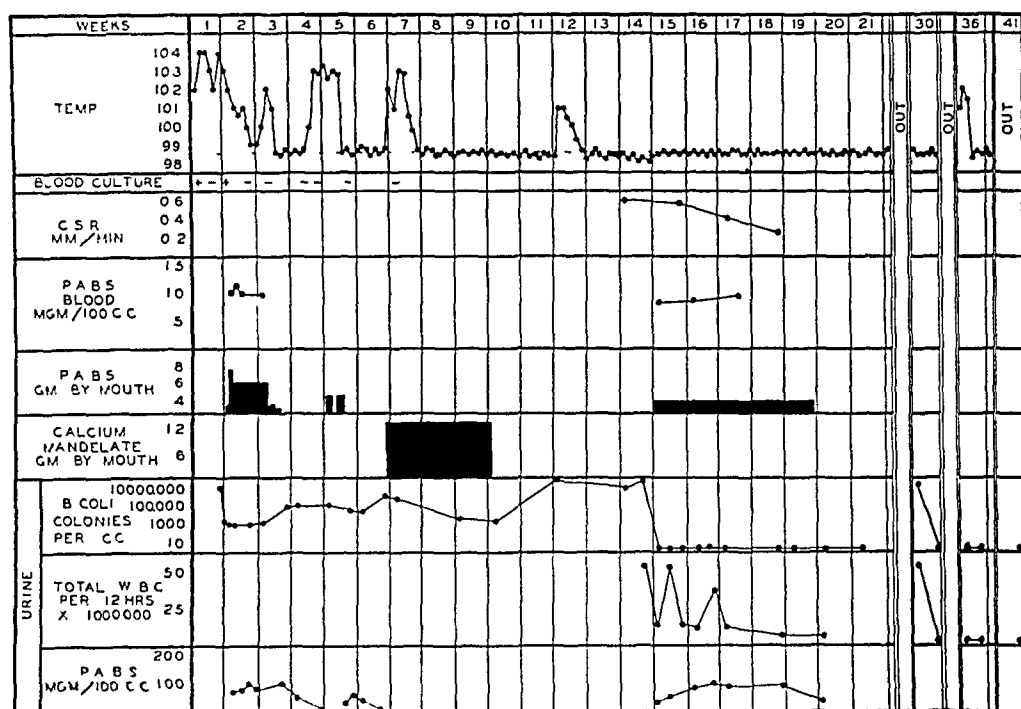


Chart 2—Course of events in case 15

The following 2 cases, presented in detail, are instructive

CASE 15—A young man was admitted to the hospital complaining of chills, fever and malaise after the passage of a urethral sound, which had been introduced in the course of an investigation of the sterility of his wife. There was a history of gonorrhea, but he had never had any previous infection referable to the renal system. The physical examination suggested the presence of an acute right-sided pyelonephritis. The urine contained many white blood cells, and the blood and urine cultures were positive for the colon bacillus. Subsequent retrograde pyelograms revealed that the pelvis of the left kidney was double, but the urine from this kidney was normal. The urine from the opposite ureter showed a very great number of leukocytes and bacteria. The course of the patient's illness is illustrated in chart 2.

The administration of sulfanilamide in doses of 5 Gm per day was begun shortly after the patient's admission to the ward and was followed by clinical improvement, the temperature returned to normal, the blood was sterile on cul-

ture and there was marked reduction of the total number of bacilli in the urine. The development of anemia prompted the discontinuance of this medication. Fever and all other symptoms recurred within five days. The exhibition of the drug was again followed by very marked clinical improvement, although there was practically no effect on the number of excreted bacteria. The use of sulfanilamide was therefore again discontinued. Another acute exacerbation of the disease followed but subsided without medication. The administration of 12 Gm of ammonium mandelate per day, under controlled conditions which caused the excretion of an acid urine of limited volume, was begun, and it was continued for fifteen days without significant effect on the persisting evidences of infection.

Since the patient failed to return to full health and the urine continued to contain many white blood cells and bacteria, sulfanilamide was again exhibited, in a dose of 3 Gm per day, for five weeks. With this regimen the urine became sterile within twenty-four hours, the excretion of cells and the erythrocyte sedimentation rate returned to normal and the patient gained weight and felt well.

One month after discharge from the hospital the patient suffered a severe attack of cystitis, with bacilluria, which subsided promptly without medication. Two months later there was a brief period of pain in the perineum and fever of undetermined origin. After that time he remained absolutely well until recently, eighteen months after the acute onset, when the cystitis recurred, accompanied by bleeding after micturition.

It was of considerable interest that sulfanilamide in large doses failed to sterilize the urine in the early stages of the illness, although its administration was apparently accompanied by clinical improvement and sterilization of the blood. Later, after the acute phase had subsided, a smaller dose of the drug was followed by immediate sterilization of the urine, with a concomitant gain in weight and return to good health. Three subsequent events, cystitis on two occasions and an undiagnosed fever with pain in the region of the perineum, suggested that the infection was not eradicated from the genitourinary tract at the completion of the final course of sulfanilamide, but each attack has subsided uneventfully. The course has indicated that no infection remains in the kidney but that the prostate gland is still the site of active disease.

It should be pointed out that anemia developed during the use of the drug in the acute phase of the disease but did not recur when the drug was exhibited later, after the temperature became normal, for a prolonged period.

CASE 16—A woman of 53 was admitted to the hospital with a history of chills, fever and malaise for a short time but without localizing signs or symptoms of infection except for a few rales at the base of the right lung. There was no history of any previous acute illness. Retrograde pyelograms revealed a normal left kidney and some deformity of the superior calix of the right kidney. The patient's course in the hospital is illustrated in chart 3.

Bacilluria was present during the patient's second week in the hospital but sulfanilamide was not used until a colon bacillus bacteremia was discovered during the fourth week. The administration of the drug was followed by a fall in temperature and reduction in the number of organisms in the urine, but the blood

was not sterilized and the development of moderate anemia suggested the withdrawal of the drug. This event, however, was followed by such a severe exacerbation of all symptoms and signs that sulfanilamide was again given, but this time it had no effect on the course of the disease. The patient died in the seventh week of her illness.

Autopsy revealed a normal right kidney. In the left kidney there was a small stone in the inferior minor calyx, the mucosa of the pelvis was greatly inflamed and was sloughing, throughout the cortex there were a number of small abscesses, and there was thrombophlebitis of the small renal veins.

This case again suggests that sulfanilamide may favorably influence the course of acute pyelonephritis without sterilizing the urine, as evidenced by the apparently good effects of the drug when it was first used.

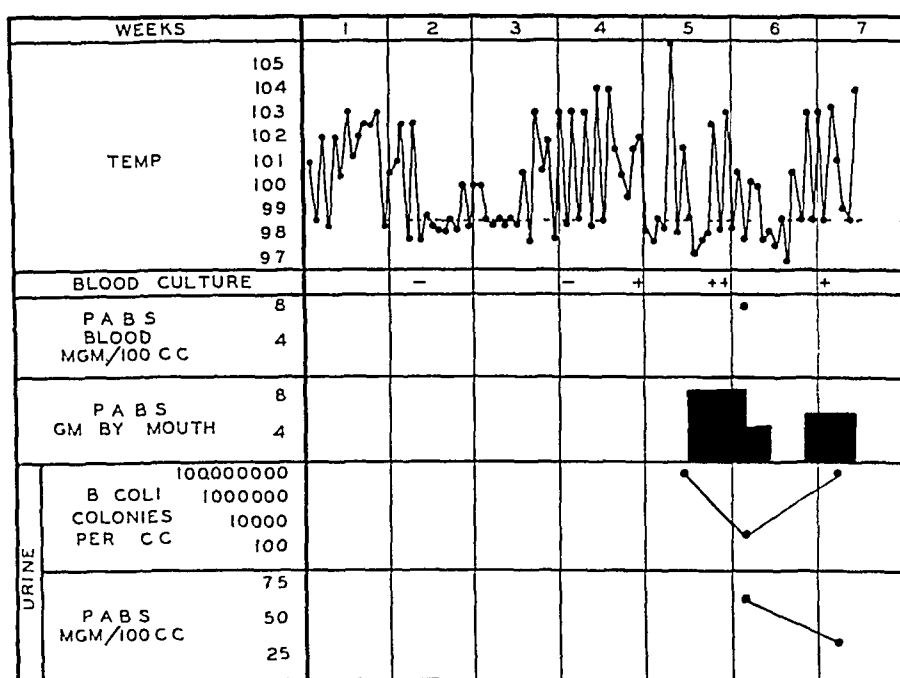


Chart 3—Course of events in case 16

That it should have been discontinued is unfortunate, but it is doubtful that the patient could have ever recovered without removal of the kidney, in the light of the existing thrombophlebitis of the intrinsic renal vessels.

The course of the disease in this instance emphasizes the fact that severe acute infections of the kidney are potentially of grave significance and should be managed with great care. The gradual development of moderate anemia in those instances in which the course of the illness appears to be favorably influenced by the use of sulfanilamide is not a definite indication for the withdrawal of the drug, at times it may be wise to combat the lack of red blood cells by transfusion with whole blood, meanwhile continuing therapy with sulfanilamide.

Comment—Six cases of acute pyelonephritis without a previous history of infection of the urinary tract were studied. In 2 the administra-

tion of sulfanilamide after the subsidence of the initial acute phase of the disease was followed by sterilization and clearing of the urine. In 2, the drug was given during the height of the illness and a dramatic clinical improvement, with rapid fall of temperature and sterilization of the urine, occurred. In 1 case, clinical and bacteriologic relapse was immediately controlled by reexhibiting the drug, a second mild relapse, associated with the presence of *Staph. albus* in the urine, was not affected. Three patients were available for further studies and were found to be well, with sterile urines, after intervals of from one to six months.

Two additional cases presented important features. In both, very marked clinical improvement followed the exhibition of the drug during the acute stage of the disease, with a definite reduction in the number of bacteria in the urine but without their elimination. In 1 case, a second course of the drug sterilized the urine promptly, although adequate mandelic acid therapy had previously failed to accomplish this result. It is impossible to assess exactly the effect of sulfanilamide on the outcome in this case, but it does seem definite that the drug favorably altered the course of the acute illness, and that later it was of great assistance in the eventual eradication of infection in the kidneys and in clearing the urine of bacteria. The fact that the blood became sterile on culture should not be interpreted as a definite effect of the drug, since such bacteremias are notoriously transient.⁸

The influence of the drug in the last case is impossible to evaluate. Clinical improvement and reduction of the total bacilluria accompanied the use of the drug but the blood culture remained positive. The result of its unfortunate withdrawal may suggest that had it been used continuously a favorable outcome would have been possible, but in the light of the observations at autopsy this is unlikely. Certainly infection of the kidneys by the colon bacillus may be expected to be so extensive or so complicated by various factors that death will ensue regardless of the type of therapy instituted.

Group 3. Acute Exacerbation of Chronic Infections of the Urinary Tract—Cases 10 and 11 are examples of exacerbations of long-standing chronic cystitis with other disease as a complicating factor. The administration of sulfanilamide in these instances failed to sterilize the urine and was followed by symptomatic improvement in the second case only. In the latter the patient when seen one year later had been well, but his pyuria and bacilluria persisted.

The effect of this drug in cases of acute pyelonephritis following previous chronic infections is illustrated by cases 12, 13 and 14. The first

⁸ Keefer, C. S., and Felty, A. R. *Bacillus Coli Sepsis. Clinical Study of Twenty-Eight Cases of Blood Stream Infection by Colon Bacillus*, J. A. M. A. 52: 1430 (May 3) 1924.

case it that of a young woman who had suffered from subacute to chronic cystitis for four years and who was admitted to the hospital with a severe recurrent infection of the kidneys, which subsided rapidly. Sulfanilamide therapy directed at the residual bacilluria and pyuria failed to sterilize the urine, although the patient became clinically well.

Case 13 is that of a young woman with decompensated rheumatic heart disease and chronic pyelonephritis of several years' duration. An acute exacerbation developed in the hospital and failed to respond to the usual therapeutic measures. A course of sulfanilamide, given by mouth, was instituted. Because of the depressed renal function (the standard urea clearance was only 30 per cent of normal) the concentration of the drug in the blood rose rapidly, and medication was stopped after four days. The concentration of sulfanilamide in the urine was high, and marked relief of all symptoms and sterilization of the urine took place. One year later she was found to have bacilluria and to suffer from frequent attacks of pain in the flanks, with fever.

The next case in table 1 (case 14) is that of a man, 27 years of age, who had a history of recurrent attacks of cystitis and pyelonephritis dating from childhood. He was severely ill on admission, with pain in the flank, fever, bacilluria and pyuria. All of these symptoms were readily controlled within a few days after exhibition of the drug, although bacteria continued to be present in the urine in small numbers. He was well when discharged, but he returned within two weeks in a relapse identical with the previous attack. Again the institution of sulfanilamide therapy was followed by rapid clinical improvement and sterilization of the urine. Adequate doses of mandelic acid were given for two weeks. When the patient was seen three months later, he was well and his urine was normal.

The following report presents in greater detail the course of the illness in a patient who suffered repeated attacks of infection in the right kidney.

CASE 17—A young woman was admitted to the hospital in November 1937 suffering from chills, fever, pain in the abdomen and the right flank and dysuria. The urine showed bacilli and pus. There was a history of several similar episodes. Since rest, the administration of fluids in large volume and an adequate trial of therapy with mandelic acid failed to clear the urine, and since retrograde pyelography revealed abnormal movement of the right kidney, with dilatation of the renal pelvis, right nephropexy was performed.

Convalescence was uneventful, but the patient was readmitted to the medical wards with a clinical picture identical with that on her previous entry. The course of her illness after that time, with pertinent data, is illustrated in chart 4. She improved rapidly on a regimen of rest and administration of large volumes of fluids. Three grams of sulfanilamide per day were given by mouth in two courses, and the bacilluria and pyuria rapidly disappeared. Organisms and cells reappeared in the urine promptly on the withdrawal of medication, and during

the second attack clinical relapse also was observed At this time the urine was acidified and 12 Gm of calcium mandelate was given daily for five weeks Moderate pyuria and bacilluria continued The patient was discharged, only to return in three weeks with complaints similar to those on her previous entries

A trial of very large doses of sulfanilamide was considered advisable at this time, so 8 Gm was given daily for fifteen days The fluid output was limited to 1,500 cc , a high concentration of the drug in the urine and blood, a return of the urine to normal and clinical improvement were thus attained There was no reaction to the drug except slight headache One week after withdrawal of sulfanilamide large numbers of bacteria and cells were to be found in the urine, although the patient felt well Thirteen weeks later she was reexamined The renal function was normal and the pyuria was minimal, but organisms could be

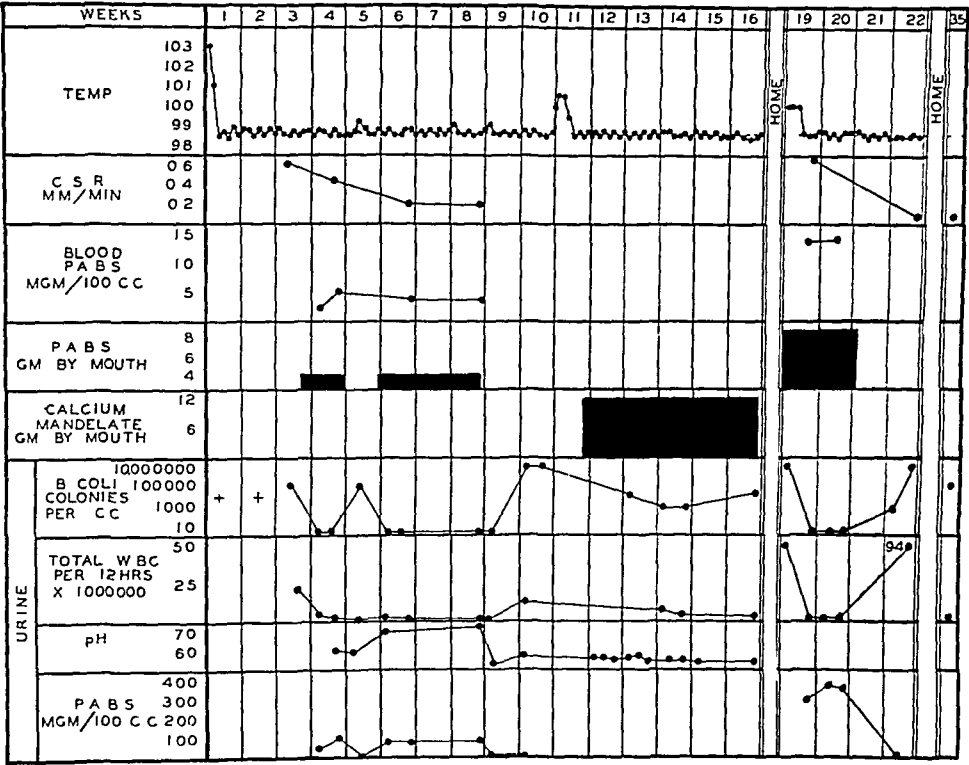


Chart 4—Course of events in case 17

isolated from the urine and she suffered frequent mild attacks of pain in the right flank

This case illustrates the ease with which the evidences of disease may be eliminated in a patient who suffers from repeated attacks of urinary tract infection and the difficulty of bringing about a permanent cure by the use of sulfanilamide It is also of interest and importance that two courses of calcium mandelate, under excellent control, failed entirely to eliminate bacteria from the urine

Obstruction of the right ureter, of unknown cause, was undoubtedly the underlying process responsible for the continuing difficulty in this patient, but it is impossible to determine whether her repeated episodes

were the result of exacerbations of persisting chronic infection or of reinfections in a kidney more than normally susceptible to disease. The return of the excretion of white cells and of the sedimentation rate to within normal limits suggests, but in no sense proves, the latter hypothesis.

Comment—Sulfanilamide failed to sterilize the urine in 3 cases of patients suffering acute exacerbations of chronic urinary tract infections, although the dosage and the concentration of the drug in blood and urine were similar to those in other cases in this study. In 3 other cases bacteria disappeared from the urine, but they were known to have reappeared in 2, and in the third mandelic acid was also used to effect a more permanent result. In 2 instances clinical relapse was also observed on one or more occasions. Treatment with sulfanilamide was followed in every case but 1 by rapid and striking clinical improvement, both in the initial phase and in relapse.

It is well known that a history of repeated infection of the urinary tract militates against the possibility of eventual permanent cure, as relapse and reinfection are notoriously common regardless of the methods of therapy used. These data suggest that, in so far as sulfanilamide is concerned, initial sterilization of the urinary passages may also be more difficult than in cases without such a history and, as is to be expected, the final results may not be wholly satisfactory.

Group 4 Marked Congenital Abnormality of the Urinary Passages—One case in this classification, that of a young man admitted to the hospital in the acute phase of a very severe pyelonephritis, has been studied. Hypospadias was present, and retrograde pyelography revealed marked congenital abnormalities, with dilatation of the right pelvis and rotation of the left kidney, but there was no history of any previous acute episode. The administration of sulfanilamide was begun on the first day in the hospital, there was a rapid return of the temperature to normal, the urine was sterile within five days and the patient was discharged, well. He has not been seen since that time.

Comment—Sulfanilamide was effective in relieving the symptoms and sterilizing the urine of a patient with marked congenital abnormalities of the urinary tract.

CRITERIA OF CURE

It became evident early in this study that in certain instances the urine was very easily sterilized and pyuria markedly reduced after the oral administration of sulfanilamide. A few simple tests were then applied to a group of patients to determine whether such tests could be utilized as measures of the adequacy of therapy and permanence of cure. The procedures thought to be of the greatest potential value were determination of the sedimentation rate of the erythrocytes by the method of

Rourke and Ernstene, and estimation of the twelve hour excretion of white cells in the urine, by the method of Addis. The sedimentation rate is well established as a measure of tissue destruction within the body,⁹ and the disappearance of pyuria has been used for many years as a criterion of healing of infections of the urinary tract. The results of these studies are summarized in table 2.

The sedimentation rate of the erythrocytes was measured in 6 patients at the completion of a course of therapy with sulfanilamide and was found to be within the normal limits of 0.35 mm per minute in every instance. It had been elevated previously in all instances in which the determination was made during the acute illness. Two patients had remained well for intervals of seven and forty-five days, 2 had suffered attacks of acute

TABLE 2—*Evaluation of Sedimentation Rate of Blood and Excretion of Leukocytes in Urine as Criteria of Results of Treatment*

Case	Sedimentation Rate, Vm per Min		No. White Blood Cells in Urine per 12 Hours		Follow Up	
	Before Treatment	After Treatment	Before Treatment, Million	After Treatment, Million	Days	Results
1			450,000,000	13,000,000	30	Well urine sterile
6			21,000,000	2,600,000	180	Well urine sterile
7	1.60	0.35			45	Well urine sterile
8	0.71	0.20	74,000,000	3,000,000	5	Mild cystitis
9	1.60	0.15	15,000,000	1,500,000	7	Well urine sterile
13			450,000,000	3,000,000	180	Innumerable B. coli in urine
14		0.20		7,500,000	14	Severe acute relapse
15	0.65	0.27	64,500,000	4,000,000	45	Acute cystitis
			1,200,000,000	5,000,000	120	Well urine sterile
17	0.59	0.25	18,000,000	500,000	30	Relapse
	0.98	0.10	45,000,000	200,000	5	Relapse

cystitis, and 2 had severe clinical and bacteriologic relapse in the course of an acute pyelonephritis.

The excretion of white blood cells was studied in 8 patients. In 5 it was found to be within the normal limit of 3,000,000 cells per twelve hours. Of these, 2 were still well when last seen, in 1 cystitis had developed and 2 had suffered frank clinical and bacteriologic relapse, similar to the initial infection. Of those with abnormal excretion of cells, 1 has remained well, 1 has had a very severe cystitis and in 1 a very severe pyelonephritis developed within fourteen days after he left the hospital.

Case 17 is of interest because results of both tests were normal on two occasions after the exhibition of sulfanilamide, yet severe active infection of the kidney developed after withdrawal of the drug on each occasion, once within thirty and once within five days.

⁹ Ham, T. H., and Curtis, F. Plasma Fibrinogen Response in Man, *Medicine* 17: 413, 1938.

Comment—It is possible to conclude from these results that the disappearance of all signs of infection from the urinary passages, as evidenced by the return of the sedimentation rate and excretion of white cells to normal, does not guarantee a permanent cure of the disease, nor can these tests be used to determine effectively the optimum time for the cessation of therapy

TOXIC EFFECTS OF SULFANILAMIDE

Minor toxic effects of the administration of sulfanilamide—cyanosis, headache, anorexia and malaise—have been repeatedly reported and were noted in nearly every case during the course of this study. In nearly all of the patients who were treated during the acute phase of their infection a slowly progressing anemia developed, without jaundice, with red blood cell counts falling to approximately 3,500,000 and hemoglobin contents to 65 per cent (Sahli). Several of these patients received the drug for prolonged periods and in comparable doses later, after the febrile period had passed, either without progression of the anemia or, if the blood had returned to normal, without its redevelopment. This would suggest that the presence of an acute febrile illness is in part responsible for the development of this complication. In certain instances, if the anemia seemed alarming, transfusions of whole blood were given and the use of the drug was continued. In others the diminution of red cells seemed to cease spontaneously at a certain level. In a third group the medication was withdrawn.

In 1 case a marked apathy and malaise was noted but none of the other complications reported by other authors were observed.

FACTORS INFLUENCING THE CLINICAL RESULTS

It is evident from the clinical results outlined previously that great differences exist in regard to the ease with which infections of the urinary tract can be initially eradicated and to the permanence of the eventual cure, for those patients who had previous histories of similar episodes were more difficult to relieve initially and to maintain in a state of health.

It is important to determine whether there are differences in the treatment of these patients or demonstrable factors in the patients themselves to account for these variations. The clinical facts have been examined with this in mind, and no striking differences between these patients have been demonstrated. All received similar basic treatment, with restricted activity and the administration of large volumes of fluid. The urinary output was recorded, the average was from 2,500 to 3,500 cc per twenty-four hour period in each case. The dosage of sulfanilamide varied from 2 to 8 Gm, the usual amount being 3 Gm per twenty-four hour period, in divided doses. The maximum observed concentrations of the unacetyl-

ated drug were from 2.5 to 13.7 mg per hundred cubic centimeters in the blood and from 23.0 to 363.8 mg in the urine. Medication was continued for from four to thirty-five days, but it is impossible to correlate the variation in time with any essential differences among the various groups. Naturally, it is true that the patients with more refractory infections received larger doses, attained higher levels of the drug in the blood and urine and were maintained on treatment for longer periods of time than those in whom a satisfactory result was obtained easily.

As Long¹⁰ has suggested, larger doses and higher concentrations of the drug in the body fluids might have effected a sterilization of the urine in those cases in which this result was not obtained. In one case in which the medication was irregular this almost certainly was true. Nevertheless, amounts of the drug effective in some cases were ineffective in others, and in 2 instances large doses and high levels easily sterilized the urine but relapse occurred almost at once after withdrawal of the drug.

Physically the individual patients presented no striking differences except for the presence of pregnancy in one group, congenital malformation of the urinary passages in another, Hodgkin's disease in 1 patient, and diabetes mellitus in another. Retrograde pyelograms were taken regularly only when the infection was refractory to treatment, but they were approximately normal in every instance except cases 9 and 17.

In the light of these facts—that certain persons suffering from infections of the urinary passages present a disease state which is difficult both to control initially and to eliminate entirely by the use of sulfanilamide, and that striking differences either in therapeutic regimen or in the patients themselves are absent—a third possibility was suggested. This was that there might be a marked difference in the sensitivity of the various strains of infecting organisms to the drug, and this hypothesis was tested *in vitro*.

STUDIES ON THE COLON BACILLUS *IN VITRO*

Seven strains of *Bacillus coli* recovered from the patients previously described in this report were studied *in vitro* to determine whether there might be demonstrable individual differences in the organisms which made them less susceptible to the action of sulfanilamide. It was also desirable to know the minimal concentration of the drug that would cause maximum bacteriostasis. Long¹⁰ has noted differences in the sensitivity of various strains, but he has maintained that if large doses of the drug are given and a high concentration of the drug in the urine is obtained better clinical results will follow in those instances in which refractory strains have been present in the urine.

10 Long, P. H., and Bliss, E. Observations on the Mode of Action and Clinical Use of Sulfanilamide in Urinary Tract Infections, *South M. J.* **31** 308, 1938.

Methods—The organisms were grown for eighteen hours in ordinary veal infusion broth and diluted in tenfold steps in the medium to be studied, since Mellon¹¹ reported greater activity of the drug when diluent and test substance were urine. Agar pour plates were made with 1 cc amounts of the various dilutions before and after a twenty-four hour period in the incubator, to obtain initial counts of the organisms and to determine the effect of the drug. Preliminary studies had revealed that the amount of sulfanilamide transferred to the plate with the medium would not affect the growth of the colon bacillus.

The urine used in certain instances was passed through a Berkefeld filter to insure sterility. Sulfanilamide was added in suitable amounts from an 0.8 per cent solution. When mandelic acid was used, it was added to the urine in the crystalline form, by weight.

Since Helmholtz had suggested that the action of the drug in vitro is greater if the medium is alkaline, many of the tests were performed at various levels of p_H , from 5.5 to 8. In those involving mandelic acid, the urine was adjusted to p_H 5.5 after the addition of the acid.

Effect of Sulfanilamide in Veal Infusion—A preliminary study of 4 strains of *B. coli*, grown and diluted in ordinary broth at p_H levels of 5.5, 6.5, 7.5, and 8 and at concentrations of sulfanilamide of 40, 80, and 160 mg per hundred cubic centimeters, revealed no bacteriostatic or bactericidal effect of the drug in 3 instances and very slight inhibition of growth in the fourth.

Effect of Sulfanilamide in Urine—After demonstrating the apparent inactivity of the drug against 4 strains of *B. coli* in broth, we studied the same strains in urine of varying p_H and at different concentrations of the drug, to evaluate the possible effects of these two variables. The results are presented diagrammatically in chart 5.

Strains 1 and 2 were most susceptible to the action of the drug, and very marked bactericidal action was demonstrated. As many as 100,000 organisms of strain 1 were killed and as many as 10,000 of strain 2. The tests with strains 3 and 4 revealed very clearly the bacteriostatic activity of the drug, but only a few organisms were killed.

It is of great interest that no significant effect of p_H was demonstrated and that with these strains a very much greater increase in the effectiveness of the drug was noticed when its concentration was raised from 40 to 80 mg than when it was raised from 80 to 160 mg. The latter increase in concentration failed in every instance to produce a significant increase in either bacteriostatic or bactericidal effects. With strains 3 and 4, even when the concentration of the drug was raised to 320 mg no additional inhibition of growth was observed.

Since it was possible that the urine might be more bacteriostatic than the amount of uncombined sulfanilamide present would suggest, owing to

11 Mellon, R. R., and Shinn, L. E. Potentiating Influence of Urine on Sulfanilamide's Bacteriostatic Effect on *E. Coli* in Vitro, *Proc. Soc. Exper. Biol. & Med.* **37** 331, 1937.

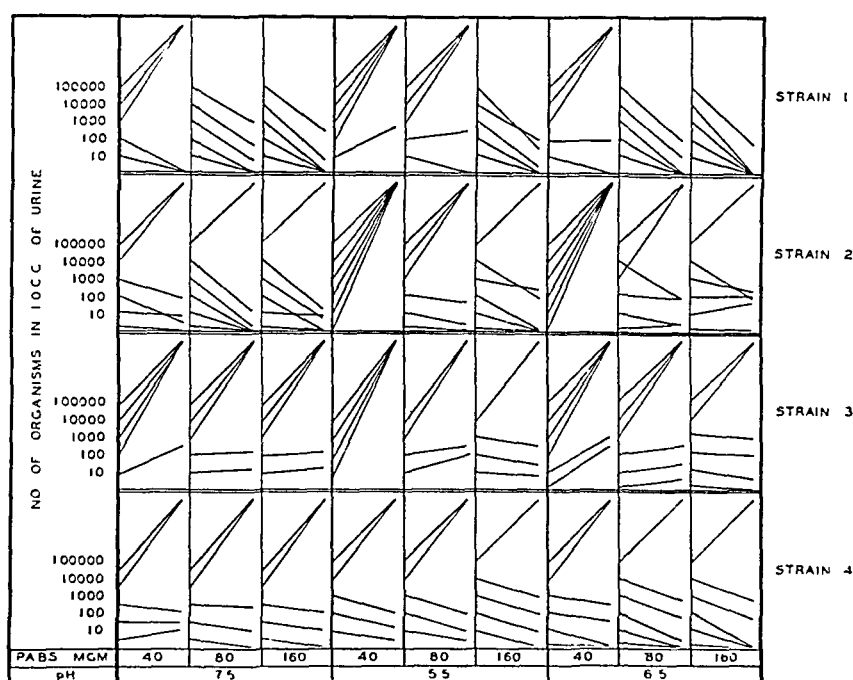


Chart 5—Effect of sulfanilamide, in varying concentrations and at different p_H , on 4 strains of colon bacillus isolated from patients with infections of the urinary tract. Strain 1 was isolated from the patient in case 3, strain 2, from a patient not discussed in this paper, strain 3, case 17, strain 4, case 8.

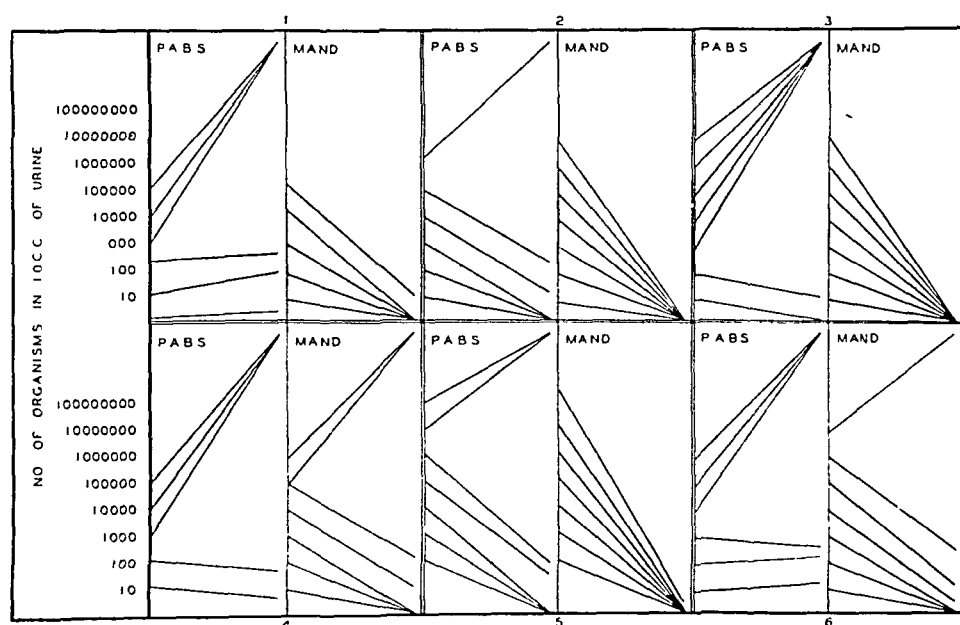


Chart 6—Comparative effects of sulfanilamide and mandelic acid on 6 different strains of colon bacillus. The concentration of sulfanilamide was 160 mg per hundred cubic centimeters of urine, and that of mandelic acid was 1000 mg, the p_H was 5.5. Strain 1 was isolated from the patient in case 8, strain 2, case 1, strain 3, case 15, strain 4, case 13, strain 5, case 3, strain 6, case 17.

the presence of an equal amount of the acetylated compound, these same strains were tested in two samples of urine from a patient to whom the drug had been administered by mouth. One specimen contained 81.0 and 37.8 mg, per hundred cubic centimeters of the combined and the free form, respectively, the other, 150.0 and 93.6 mg, respectively. Each strain was studied at different levels of p_H , and in every instance the results were exactly comparable to those of the previous tests, the entire activity of the drug was apparently in its unacetylated form, as had been previously reported¹²

Six strains of *B. coli* isolated from patients under observation were studied in urine with the concentration of sulfanilamide 160 mg and the p_H 6.5 and, as a comparison, in urine with the concentration of mandelic acid 1 per cent and the p_H 5.5. The results of these experiments are depicted graphically in chart 6.

Sulfanilamide had marked bactericidal effects only on strains 2 and 5. No marked differences were observed among the other 4 strains, the demonstrable effect was moderate bacteriostasis.

Clinically, the urine in 5 of these patients was sterilized with ease, the concentration of the drug in the urine being less than 100 mg in every instance. In the sixth (case 3) a very great reduction in the total number of organisms excreted took place at a time when the urinary concentration was 23.0 mg.

Two of the strains under discussion, 4 and 6, were isolated from patients in whom unsatisfactory clinical results were obtained, in the sense that relapse occurred in each. Yet neither of these organisms *in vitro* appeared to be more refractory than the others studied.

The studies conducted with mandelic acid, under conditions comparable to those existing in the urinary passages, are also very striking. Chart 6 shows that with every strain this agent was much more effectively bactericidal than sulfanilamide, since from 100,000 to 1,000,000 organisms were killed in every instance, with some variation among the strains.

Clinically, however, this drug was administered to 2 patients (cases 15 and 17), under controlled conditions, with only minimal reduction of the number of organisms in the urine. Subsequent exhibition of sulfanilamide readily sterilized the urine in these persons. This is suggestive evidence that the modes of action of sulfanilamide and mandelic acid are different and also that *in vitro* studies are liable to give a false impression as to the relative values of urinary antiseptics.

Comment—It has been possible to demonstrate certain facts by these studies on the colon bacillus *in vitro*. Sulfanilamide is bacteriostatic or bactericidal for this organism, most markedly so when the concentration

12 Marshall, E. K. Bacterial Chemotherapy. The Pharmacology of Sulfanilamide, *Physiol. Rev.* **19**: 240, 1939.

of the drug is approximately 80 mg or more per hundred cubic centimeters. Increase of concentration above this level does not strikingly improve the action of the drug. No effect of p_H on its activity was demonstrable. Definite differences exist in the relative sensitivities of various strains of *B. coli* to the drug, but clinical sterilization of the urine occurs at levels which are only bacteriostatic in vitro and no correlation was observed between the in vitro and the clinical results in those instances in which unfavorable therapeutic effects had been observed.

Mandelic acid is much more actively bactericidal than sulfanilamide in vitro, yet in these studies it was much less satisfactory for sterilizing the urine in vivo.

GENERAL COMMENT

To understand the action of urinary antiseptics it is necessary to review some aspects of both the pathology of pyelonephritis and the mechanisms by which infection may reach the kidney.

Pathologic investigation of this type of renal infection has shown¹³ that there is primarily an involvement of the lymphatic system of the organ. In many instances inflammation and necrosis of the epithelium of the pelvis and calices occurs, but, in addition, there is always widespread inflammation between the tubules and glomeruli, with cellular infiltration and very often small abscesses in these areas, from which bacteria may be recovered. Healing is regularly accompanied by scarring and contraction of the kidney.

The manner in which the infecting organism is able to reach the kidney and the mechanisms responsible for maintaining the disease have long been the subject of debate. It is generally agreed that obstruction to the free flow of urine predisposes this organ to infection. The principal source of disagreement is the question of whether the organisms reach the kidney by way of the blood stream or ascend from the lower urinary passages. Such arguments are highly academic, especially in the light of recent experimental evidence which indicates that in the presence of urinary obstruction intravenous or intraureteral injection of the colon bacillus in the rabbit will produce renal lesions practically identical with those of human pyelonephritis.¹⁴

In summary, then, pyelonephritis is an infectious process which involves the entire kidney rather than the superficial tissues of the pelvis, and to which there is a predisposition in the presence of obstruction to the free flow of urine. It is fair to assume that most of the patients described in this report suffered from disease of this nature.

13 Weiss, S, and Parker, F, Jr. Pyelonephritis. Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18** 221, 1939.

14 Mallory, K. Personal communication to the authors.

In the light of these facts, it is obvious that to regard the infected urinary passage as a container of urine, to be sterilized by the excretion into it of a bactericidal agent, is too superficial, since much of the infectious process lies deep in the renal tissue, far removed from the urine. One might postulate that the drug-containing urine is reabsorbed by the renal lymphatic system, but this is a somewhat unlikely hypothesis. The dramatic results of the administration of sulfanilamide, which frequently include sterilization of the urine in spite of only bacteriostatic or moderately bactericidal effects *in vitro* suggest that the action of the drug in the patient is more complex than in the test tube.

It is certainly true that the infection in the parenchyma of the kidney must be cleared by the same cellular and immune mechanisms responsible for the healing of inflammatory processes elsewhere in the body. The effectiveness of the therapeutic agent here is limited to that degree of bacteriostasis which it is able to exert in those concentrations in which it is brought to the tissues by the blood stream.

In view of these observations, it seems likely that an agent which *in vitro* exerts marked bacteriostasis or bactericidal effects against the organisms responsible for an infection of the urinary passages has a threefold mode of action in the infected kidney.

First, the presence of the agent in the urine inhibits the multiplication of the organism in the tubules, pelvis, ureter and bladder, and may destroy it. It is possible that those membranes in direct contact with the urine may absorb a sufficient amount of the drug for this effect to occur in their most superficial layers. The direct result of this action will be decreased production of toxin in the urinary tract, with consequent reduction of superficial inflammation, congestion and edema and, in turn, resultant relief of symptoms and decrease in obstruction to the urinary flow. Water diuresis, long known to affect favorably the course of these infections, acts in a similar but less dramatic manner by washing away the organisms from these areas.

Second, the elimination of obstruction and the inhibition of multiplication of the bacteria in the urine must markedly reduce the possibility of the reinfection which undoubtedly occurs in the deeper renal tissues when the tubules are engorged and the organisms are multiplying freely.

Third, depending on the possible relationship of the effect of the drug to its concentration in the blood, there may be direct action on the organisms in the deeper tissues, slowing their multiplication and permitting the usual clearing mechanisms to operate more effectively. This action may be important in its effect on the colon bacillus, since these organisms are usually so weakly invasive that even a very slight reduction in the rate of

increase of the bacteria might be adequate to enable the tissues to eliminate them

It is, then, probable that final recovery from infections of the kidney results from the activity of the immunogenic mechanism of the body, which may be aided by certain chemical agents. In support of this theory are the facts that most acute renal infections are self limited and that healing is complete, in the absence of obstruction, even though no special therapy is instituted. Relapse in the presence of obstruction may very well be due to repeated reinfection. Chronic infections without demonstrable obstruction, such as are described in this paper, are extremely difficult to relieve with any drug, this fact suggests that the bacteria continue to remain viable and multiply in the tissues because of some unknown defect in the mechanism by which the body usually removes infecting agents.

From the study of the sensitivity of different strains of *B. coli* which were isolated from the urine of patients with pyelonephritis the following facts emerged. When the bacteria were incubated at different p_H levels in veal infusion broth which contained varying concentrations of sulfanilamide it was not possible to demonstrate that the drug had either a bacteriostatic or a bactericidal effect. However, when the same strains were studied in sterile urine which contained sulfanilamide the results were different, in all instances there was bacteriostasis and on 2 strains the drug had definite bactericidal effects. It was of interest that varying the p_H of the urine seemed to produce no significant difference in the action of sulfanilamide. The concentration of the drug, on the other hand, was of the highest importance. The most striking increase in the efficacy of the drug occurred when the concentration was increased from 40 to 80 mg, there was little demonstrable increase in the action of the drug when higher concentrations were used. The study also confirmed the observation of other workers that in samples of urine which contain both the free and the acetylated form of sulfanilamide the free form is the active principle.

It was of interest to compare the results in vitro with those in vivo. It was found that in 5 of the 6 cases in which bacteria were cultured and tested in vitro, administration of sulfanilamide in vivo sterilized the urine, the concentration of the drug in the urine was less than 100 mg in every case. In the sixth case, a great reduction in the total number of organisms excreted took place at a time when the concentration of the drug in the urine was only 23 mg. These observations indicate that in the test tube it is possible to show bactericidal effects of sulfanilamide on only a few strains of *B. coli*, and on other strains the effect is merely bacteriostatic. On the other hand, when the drug is given to patients it often

prevents the growth of organisms in the urine. This suggests that the action in the body is different from that *in vitro* and that there are extra-pharmaceutical factors to account for this difference.

When the effects of mandelic acid and of sulfanilamide on the same strains of *B. coli* *in vitro* were compared, it was found that mandelic acid in 1 per cent concentration at a p_H of 5.5 was a much more effective bactericidal agent than sulfanilamide, since from 100,000 to 1,000,000 organisms were killed in every instance. There was some variation in resistance among the strains. However, when mandelic acid was given to patients it brought about only a minimal reduction of the number of organisms in the urine. Here the evidence again suggests that the mode of action of the drug is different *in vivo* and *in vitro*, and that *in vitro* studies are liable to give an erroneous impression as to the relative values of urinary antiseptics.

SUMMARY

A study of treatment with sulfanilamide in 17 cases of infection of the urinary tract due to *Bacillus coli* is presented. Clinical improvement and sterilization of the urine were easily accomplished in most instances, the best results were obtained in those cases in which there was no previous history of infection of the urinary tract and in those in which the infection was associated with pregnancy. If evidence of chronic infection of the urinary passages was present the urine was more difficult to sterilize, and clinical and bacteriologic relapse frequently occurred.

The urine usually could be sterilized by the administration of 2 to 5 Gm. of sulfanilamide in twenty-four hours by mouth, this dose resulted in concentrations of from 23.0 to 139.0 mg. of the drug per hundred cubic centimeters of urine. No definite correlation was demonstrable between the dose of sulfanilamide, its concentration in the urine and the permanence of cure. The return to normal of the number of formed elements excreted in the urine and of the sedimentation rate could not be regarded as indicative of permanent eradication of infection from the urinary tract.

The usual toxic symptoms associated with the administration of sulfanilamide were observed. Anemia regularly appeared when the drug was exhibited in the presence of fever but usually failed to recur when the drug was administered in the absence of fever.

Seven strains of *B. coli* isolated from the urines of these patients were studied *in vitro*. Sulfanilamide had marked bacteriostatic and, in certain instances, bactericidal effects on the bacteria, there were great differences in sensitivity to the drug between the various strains. Optimal bacteriostasis was obtained with concentrations of more than 80 mg. of sulfanilamide per hundred cubic centimeters of urine. To increase its

concentration above 160 mg did not significantly increase the drug's effectiveness. The p_H of the urine did not affect the activity of the drug in vitro.

No correlation was demonstrated between the activity of sulfanilamide in vitro and that in vivo. Mandelic acid in vitro was markedly bacteriostatic for all strains, but in vivo it was not as effective as sulfanilamide in sterilizing the urine.

The mode of action of urinary antiseptics in relation to the pathologic process in infections of the urinary tract is considered.

BACTERIAL ENDOCARDITIS SUPERIMPOSED ON SYPHILITIC AORTIC VALVULITIS

ALBERT L BRAUNSTEIN, M D
Resident Pathologist, Baltimore City Hospitals
BALTIMORE

AND
STUART R TOWNSEND, M D
Senior Assistant in Medicine, Montreal General Hospital
MONTREAL, CANADA

Though syphilitic aortic valvulitis and vegetative bacterial endocarditis are well established separate clinicopathologic entities, the concomitant occurrence of the two processes on the same valve has been regarded as extremely rare,¹ and relatively little has been written on this subject. In 1920 Libman² remarked on the infrequency with which bacterial endocarditis attacked valves previously altered by a syphilitic process. Thayer's³ excellent monograph on infective endocarditis gives the impression that the cases of simultaneous syphilitic and bacterial aortic valvular involvement mentioned (1 e, 4 certain cases and 2 doubtful ones) are admitted reluctantly and with a skepticism that such combinations occur. Blumer,⁴ Gross and Fried⁵ and Levine⁶ likewise merely mention 1 case each but give no further details. Review of the literature has yielded only 11 proved cases.⁷ Despite this paucity

From the Department of Pathology and the Department of Medicine, Baltimore City Hospitals

Read by title before the American Society for Clinical Investigation, Atlantic City, N J, May 1, 1939

1 (a) MacCallum, W G. A Text-Book of Pathology, ed 6, Philadelphia, W B Saunders Company, 1936, pp 695 and 701. (b) White, P D. Heart Disease, New York, The Macmillan Company, 1935, p 365

2 Libman, E, in discussion on Horder, T. Discussion on the Clinical Significance and Course of Subacute Bacterial Endocarditis, Brit M J **2**:304 (Aug 28) 1920

3 Thayer, W S. Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp Rep **22** 1, 1926

4 Blumer, G. Subacute Bacterial Endocarditis, Medicine **2** 105 (May) 1923

5 Gross, L, and Fried, B N. Role Played by Rheumatic Fever in Implantations of Bacterial Endocarditis, Am J Path **13** 769 (Sept) 1937

6 Levine, S A. Clinical Heart Disease, ed 2, Philadelphia, W B Saunders Company, 1936, p 192

7 (a) Kastner, A. Ueber Endocarditis lenta, Deutsches Arch f klin Med **126** 370, 1918. (b) Briggs, L H. Bacterial Endocarditis as a Sequel to Syphilitic

(Footnote continued on next page)

of material, we have come to think that bacterial endocarditis engrafted on syphilitic aortic valves, though not nearly as common as on rheumatic valves, occurs more frequently than has heretofore been recognized. In this connection a brief summary of the chronologic developments concerning the knowledge of rheumatic and syphilitic heart diseases will be presented, since the much earlier recognition of the pathologic changes in rheumatic heart disease and the greater frequency of bacterial endocarditis on rheumatic valves than on syphilitic valves have no doubt overshadowed the incidence of superimposed bacterial endocarditis in other valvular states.

REVIEW OF THE LITERATURE

The first record of clinical and pathologic observations in a case of bacterial endocarditis was made by Lancisi in 1707,⁸ and a little more than one hundred years later the characteristic lesions of acute rheumatic valvulitis were described.⁹ A differentiation between these two valvular conditions was first attempted in 1851 by Ormerod,¹⁰ and in 1885 Osler¹¹ observed that valves which were the seat of "malignant endocarditis" frequently showed signs of previous damage. From the early part of the twentieth century to the present time a steady stream

Valve Defects, *Am J M Sc* **164** 275 (Aug.) 1922 (c) Pineles, F. Aortenlues und Endocarditis lenta, *Med Klin* **22** 444 (March 19) 1926 (d) Cade, A. Endocardite infectieuse a marche lente greffée sur une aortite syphilitique, *Lyon med* **139** 731 (June 19) 1927 (e) Schnabel, T. G., and Leivy, F. E. Cardiac Patients with Other Associated Diseases, *M Clin North America* **15** 325 (Sept.) 1931 (f) Craven, E. B. Syphilitic Aortic Endocarditis and Superimposed Bacterial (*Streptococcus Viridans*) Endocarditis, *Am J Path* **8** 81 (Jan.) 1932 (g) Raybaud, A., Jouve, A., and Farnarier, G. Maladie de Jaccoud-Osler greffée sur une aortite chronique syphilitique, *Bull et mem Soc med d hôp de Paris* **51** 136 (Feb. 4) 1935 (h) McMillan, R. L., and Wilbur, E. L. Staphylococcic Endocarditis Superimposed on Syphilitic Aortic Endocarditis, *J A M A* **109** 1194 (Oct. 9) 1937 (i) Smith, F. J. Co-Existence of Syphilis of the Aorta and Bacterial Endocarditis, *Internat Clin* **2** 1 (June) 1937 (j) Martin, H. E., and Adams, W. L., Jr. Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis. Clinicopathological Study with Five Case Reports, *Am Heart J* **16** 714 (Dec.) 1938

8 Lancisi, cited by Perry, C. B. *Bacterial Endocarditis*, Bristol, John Wright & Sons, Ltd., 1936

9 Wells, W. C. *On Rheumatism of the Heart*, *Tr Soc Improve M & Chr Knowl* **3** 373, 1812. Corvisart, J. N. *A Treatise on the Diseases and Organic Lesions of the Heart and Great Vessels*, translated by C. H. Hebb, London, Underwood & Blacks, 1813

10 Ormerod, E. L. *Gulstonian Lectures for 1851*, London *M Gaz* **12** 529, 617 and 705, 1851

11 Osler, W. *The Gulstonian Lectures on Malignant Endocarditis*, *Brit M J* **1** 467, 522 and 577, 1885

of excellent work has appeared emphasizing strongly the "frequent association and etiologic relationship" of rheumatic valvular alterations and bacterial endocarditis¹² Since the time of Paget,¹³ bicuspid valves have often been described as being particularly disposed to implantation of bacterial vegetations¹⁴ More recently, Gross¹⁵ has indicated his belief that even "most of the bicuspid valves seen in adults owe their deformity to a previous rheumatic process"

In sharp contrast to the developments concerning the knowledge of rheumatic heart disease and its frequent sequel, bacterial endocarditis, the progress in the field of cardiovascular syphilis has been slow and relatively recent, even though syphilis itself has been known since the epidemics which occurred in the fifteenth and sixteenth centuries It remained for Francis H. Welch¹⁶ to give the first accurate descriptions of syphilitic aortitis and valvulitis in 1875 The essential facts concerning the pathologic changes are embodied in his report There are but few differences between Welch's early descriptions and those encountered today, and Osler¹⁷ commented in 1909 that this report remains "the most important communication upon the subject in English" Unfortunately, however, Welch's work was soon forgotten, but in 1885, Doehle,¹⁸ working in Heller's laboratories in Kiel, revived the interest in vascular syphilis by describing a typical case of aortitis, and in 1890 he published a very complete description of the microscopic changes Opposition to both Doehle's and Heller's views was maintained, how-

12 Horder, T. J. Infective Endocarditis, with an Analysis of One Hundred and Fifty Cases and with Special Reference to the Chronic Form of the Disease, *Quart J Med* **2** 283, 1909 Libman, E. A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis, with Particular Reference to Healing or Healed Lesions, with Clinical Notes, *Am J M Sc* **144** 313, 1912 Combs, C. F. Rheumatic Heart Disease, Baltimore, William Wood & Company, 1924 Swift, H. F. The Heart in Infection, *Am Heart J* **3** 629 (Aug.) 1928 Davis, D., and Weiss, S. Relation of Subacute and Acute Bacterial Endocarditis, *New England J Med* **208** 619, 1933

13 Paget, J. On Obstructions of the Branches of the Pulmonary Artery, *Proc Roy Med-Chir Soc* **27** 162, 1844

14 Osler, W. The Bicuspid Condition of the Aortic Valves, *Proc A Am Physicians* **1** 185, 1886 Lewis, T., and Grant, R. T. Observations Relating to Subacute Infective Endocarditis, *Heart* **10** 21 (April) 1923

15 Gross, L. So-Called Congenital Bicuspid Aortic Valves, *Arch Path* **23** 350 (March) 1937

16 Welch, F. H. On Aortic Aneurism in the Army and the Conditions Associated with It, *Med-Chir Tr* **59** 59, 1876

17 Osler, W. The Schorstein Lecture on Syphilis and Aneurysm, *Brit M J* **2** 1509, 1909

18 Cited by Conner, L. A. Development of Knowledge Concerning Role of Syphilis in Cardiovascular Disease (Frank Billings Lecture), *J A M A* **102** 575 (Feb 24) 1934

ever, until the meeting of the German Pathological Society in 1903. To quote MacCallum^{1a} (p. 695), "It was impressive and a revelation to listen to the discussion by Chiari, Benda and Marchand, of the discovery of Doehle and Heller of the syphilitic nature of these changes, and particularly to realize the perfectly characteristic and peculiar appearance of the aorta so affected. Since then everyone has recognized it at a glance." Confirmation of these observations was provided by Frankel and Much¹⁸ in 1908. They reported positive Wassermann reactions of the blood in 19 of 23 cases in which typical syphilitic mesaortitis was found at autopsy. As for the clinical diagnosis in cardiovascular syphilis, Curschmann¹⁸ was probably the first to describe the tympanitic second aortic sound so frequently identified with syphilitic aortitis, although he did not realize it at the time. However, the clinical significance of this observation as well as the signs of aortic insufficiency were not generally appreciated until after the advent of the more universal acceptance of the associated pathologic changes.

To our best knowledge the first proved case of bacterial endocarditis superimposed on syphilitic aortic valvulitis was reported by Kastner^{7a} in 1918. His patient, a 54 year old white man, had syphilis (the Wassermann reaction of the blood was positive), and he presented the typical clinical course of bacterial endocarditis. Examination at autopsy revealed syphilitic aortitis and aortic valvulitis with superimposed bacterial endocarditis. Blood cultures during life and at postmortem examination were sterile, but numerous organisms could be demonstrated on the valve by means of bacterial stains. In 1922 Biggs^{7b} reported the case of a 35 year old man who on his first admission to the hospital had syphilis (the Wassermann reaction of the blood was positive and he had a penile scar) and typical aortic insufficiency. Through the fault of the patient little antisyphilitic therapy was given, and one year later he was readmitted, with signs of bacterial endocarditis. Repeated blood cultures showed growths of nonhemolytic streptococci. Postmortem examination revealed syphilitic aortitis and valvulitis with superimposed "acute verrucose endocarditis" and contact vegetations on the anterior mitral leaflet. In the third case, reported in 1926 by Pineles,^{7c} a positive blood culture was made showing *Streptococcus viridans*, and autopsy showed syphilitic aortitis and valvulitis as well as bacterial endocarditis. Cade^{7d} added a similar case in 1929, and Schnabel and Levy^{7e} in 1931 reported the fifth case. In 1932 Craven^{7f} studied a case in which there was syphilitic aortitis with valvulitis. Postmortem cultures showing *Streptococcus viridans* were obtained from the blood and from the bacterial vegetations on the aortic cusps. There was no evidence or history of rheumatism. Raybaud, Jouve and Farnarier^{7g}

in 1935 reported a case in which a "streptenteriococcic" organism was isolated during life. The eighth case to be reported was that of McMillan and Wilbur⁷¹ in 1937. It is extremely interesting because the portal of entry was almost certainly suggested by the clinical history. The patient, a 47 year old white man, had a positive Wassermann reaction of the blood and through his own negligence was inadequately treated. Bouts of precordial pain from which he suffered were relieved by morphine, and soon the patient became addicted to the drug. In the last year of his life he administered the drug to himself intravenously, using "poorly sterilized tap water." On this, his last, readmission to the hospital, the clinical diagnoses were syphilitic aortitis with aneurysm formation and aortic insufficiency, and subacute glomerulonephritis. Bacterial endocarditis was suspected. At autopsy these diagnoses were confirmed, and a vegetative bacterial endocarditis was found on the aortic and mitral valves. A postmortem culture taken from the spleen showed a "pure growth of hemolytic *Staphylococcus aureus*." There was no evidence of rheumatic lesions on the mitral valve. The ninth case was reported by Smith⁷² in 1937. The patient was a 63 year old white man in whom septicemia developed in the course of an infection of the lower part of the urinary tract, a prostatic abscess. The Wassermann reaction of the blood was positive, and *Staphylococcus albus* was grown from material from the blood stream. In 1938, Martin and Adams⁷³ reported 5 cases in which bacterial endocarditis was associated with syphilitic aortitis or valvulitis. Only 2 of their cases could be classified as ones in which bacterial endocarditis was superimposed on syphilitic valvulitis. The Wassermann reactions were positive in both cases, and a postmortem culture of the blood in 1 case showed a growth of *Streptococcus viridans*.

Our interest in this combination of maladies was aroused by the opportunity to observe 2 such cases during the past year. We were further stimulated by the fact that investigation of our protocols revealed the presence of 7 other proved cases which were similar. These 9 cases, provide the *raison d'être* for this study.

MATERIAL

In order to obtain cases which were unimpeachable, rigid criteria for their selection were imposed. In all the cases there were histories of syphilis, positive Wassermann reactions of the blood or, when the reactions were negative, histories of antisyphilitic treatment. In the autopsy records there were descriptions of the characteristic syphilitic changes not only in the aorta but also in the sinuses of Valsalva and in the aortic valve cusps. In addition, the bacterial vegetations had to be accurately located and described, and complete descriptions given of the

valves other than the aortic to rule out especially the possibility of previous rheumatic valvular involvement. Sections taken for microscopic study included material from the aorta, the sinus of Valsalva, the aortic valve cusps and the vegetations. In this manner the syphilitic changes could be traced directly to the valve cusps on which the bacterial vegetations were superimposed. All the cases were restudied and fresh sections made. The bacteria and all the vegetations were stained by the method employed by Brown and Brenn,¹⁹ in the sections of the aorta and the aortic valves the diminution of elastic tissue and medial interrup-

TABLE 1—Analysis of 4,921 Autopsies, Showing the Distribution of Various Valvular States as Well as Bacterial Endocarditis (Acute and Subacute) on Previously Injured and Normal Valves in Association with Syphilis*

Type of Valvular Disease	Syphilitic	Rheumatic			Bicuspid	Normal		Arterio sclerosis
		With a Positive Wassermann Reaction of the Blood	With Syphilitic Aortitis and Valvulitis	Unassociated with Syphilis		With Positive Wassermann Reaction	Without Positive Wassermann Reaction	
Superimposed bacterial endocarditis (acute and subacute)	9 (3.3+%)	3† (1.6%)	4† (2.1%)	22 (11.7%)	7 (53.7%)	5	4	4
No bacterial endocarditis	258	23	4	132	6§	?	?	?
Totals	267† (99.9+%)	26 (13.8%) (Total Rheumatic—188)	8 (4.2%)	154 (81.9%)	13 (99.8+%)	4,453 (Total of Normal and Arteriosclerotic Valves)		

* Each per cent stated is that part of the total in the given column.
† This figure represents 32.6 per cent of the cases of syphilitic aortitis (i. e. 818) or 20.4 per cent of all the cases of syphilis (i. e. 1,310) among the 4,921 cases analyzed.
‡ The bacterial vegetations were located on the rheumatic valve.
§ Five doubtful cases were not included.
|| Since it was impossible to separate the normal and arteriosclerotic valves accurately, no definite totals are included here.

tions were demonstrated by Verhoeff's and Van Gieson's stains. Care was taken to exclude all cases in which it was thought that terminal bacterial invasion of the blood stream might have played a role—cases of so-called terminal bacterial endocarditis.

Among 8,700 autopsy protocols we were able to find complete records of 17 cases in which vegetative bacterial endocarditis was superimposed on syphilitic aortic valvulitis. Though we felt that all of the latter were bona fide examples, we were obliged to exclude 8 of them for lack of suitable material for microscopic study. Even if we had

19 Brown, J. H., and Brenn, L. Method for Differential Staining of Gram-Positive and Gram-Negative Bacteria in Tissue Sections, Bull. Johns Hopkins Hosp. 48: 69 (Feb.) 1931.

been able to include these additional cases, the statistics about to be presented would have been altered only slightly, since the present series of cases is practically a mirror of the cases omitted. The 9 remaining cases which we have studied were selected in the last 4,921 consecutive routine autopsies. An analysis of the observations made in these autopsies, showing the occurrence of syphilitic and rheumatic valvular diseases and their various combinations, is to be found in table 1. The percentile distribution of 58 cases of bacterial endocarditis (acute and subacute) on previously injured and normal valves is shown in table 2.

For the sake of brevity, only 1 case is presented in detail, a case of subacute bacterial endocarditis. An analysis of the other cases as well as those abstracted from the literature is to be found in tables 3 and 4. In these tables our 9 cases are numbered 12 to 20, inclusive, and the report which follows is of case 17.

TABLE 2—*Percentile Distribution of 58 Cases of Bacterial Endocarditis (Acute and Subacute) on Previously Injured and Normal Valves*

Syphilitic	Rheumatic	Bicuspid	Normal	Arterio sclerotic	Total
15.5% (9)	50.0% (29)	12.07% (7)	15.5% (9)	6.92% (4)	99.9% (58)

REPORT OF A CASE

History—N. I., a Negro aged 31, was admitted to the medical service of the Baltimore City Hospitals on Nov. 26, 1937, with complaints of shortness of breath and weakness. The family history was irrelevant. The patient had never had rheumatic fever. He was unable to date his syphilitic infection and had never had any antisyphilitic therapy. He had been in excellent health until the onset of his present illness. Five weeks prior to his admission to the hospital a chest cold developed. There was associated dyspnea, which became progressively worse. Four weeks prior to admission there was an onset of orthopnea, weakness, epigastric discomfort, and dependent edema. For three and one-half weeks before coming to the hospital he was confined to bed with the aforementioned symptoms. There were no chills or symptoms of fever.

Physical Examination—The temperature was 99.4 F (37.4 C). The pulse rate was 100, the respiratory rate 22 and the blood pressure 130 systolic and 50 diastolic. The patient appeared in acute respiratory distress with Cheyne-Stokes breathing and generalized edema. He was well developed and well nourished. Only moderate cyanosis was present. The pupils reacted to light and in accommodation. There were signs of some congestive changes at the bases of both lungs. The heart was enlarged to the right and to the left, and a gallop rhythm was noted. There were no murmurs at the base, but a musical systolic murmur was present at the apex. The liver was felt and percussed 2 fingerbreadths below the right costal margin. The spleen was not palpated. Two days later the apical systolic murmur had disappeared and a diastolic murmur was noted over the aortic region. The pulse was of the Corrigan type. There was marked edema of the abdomen and both lower extremities.

TABLE 3—*Tabulation of Essential Clinical Data on 20 Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis**

	Case																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Age	54	35	32	42	53	23	50	47	63	61	42	44	39	40	37	40	31	52	40	28
Sex	M	M	M	M	F	M	M	M	M	M	M	M	M	M	M	F	M	M	M	M
Race	W	—	W	W	W	B	W	W	W	W	B	B	B	B	B	B	B	W	B	B
Wassermann reaction of the blood†	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+	0	+	0	+	+
Wassermann reaction of the spinal fluid	—	0	—	—	+	—	0	0	—	—	—	0	0	+	0	0	+	0	+	+
Duration of syphilis in years	8	15	—	19	34	4	—	29	?	46	26	?	?	12	?	?	?	?	8	?
Antisyphilitic therapy	—	+	—	—	0	+	+	+	0	0	+	0	0	+	0	+	0	+	0	0
History of rheumatic fever	—	0	—	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0
Temperature‡	I	S	—	S	S	0	0	0	S	I	S	S	S	0	S	C	I	C	I	S
					C				C		R	C	I		I					R
Subjective sense of fever	0	+	0	—	—	0	0	+	+	0	+	+	0	0	0	0	0	0	0	0
Chills	0	+	0	+	+	0	0	+	+	0	+	+	0	0	0	0	0	0	0	0
Dyspnea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Joint pains	+	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0
Embolie phenomena	0	+	—	0	+	—	+	0	0	+	0	0	0	+	0	+	0	+	0	0
Petechiae	+	+	—	0	0	—	0	0	0	0	0	0	0	+	0	+	0	+	+	0
Clubbed fingers	0	0	0	0	0	0	0	0	0	0	+	0	+	0	0	0	0	0	0	0
Palpable spleen	—	—	—	—	0	—	+	0	—	0	0	+	0	+	0	0	0	+	+	0
Enlarged heart	—	—	—	—	0	+	—	—	—	+	+	0	+	+	+	+	+	+	+	+
Murmurs of aortic insufficiency	—	—	—	+	+	+	+	+	?	+	+	0	?	+	+	+	+	+	+	+
Varying intensities of murmurs	0	0	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0
Pulse pressure in mm Hg	—	80	—	—	85	140	—	122	43	141	134	55	60	120	110	110	80	75	180	100
Corrigan pulse	—	—	—	—	+	—	—	—	+	+	0	+	+	+	+	+	+	+	+	+
Anemia	+	+	—	—	+	—	+	+	+	0	+	+	+	+	+	+	+	+	+	+
Leukocytosis	—	—	—	0	+	—	+	+	0	0	+	+	0	0	0	0	+	+	+	0
Hematuria	—	+	—	0	+	—	+	+	0	0	0	0	0	0	+	0	0	+	0	0
Duration of endocarditis in months	12	—	—	8	1	—	10	—	½	1	1	½	6	—	2½	12	3	6	10	½
									(?)											(?)
Diagnosis ante mortem	+	—	0	0	0	0	+	0	0	0	0	0	0	0	0	0	0	+	0	0

* The dashes indicate lack of information

† The patients having antisyphilitic therapy were inadequately treated Where Wassermann reactions of the blood were stated as being negative there were histories of treatment

‡ Abbreviations regarding temperature indicate intermittent, septic, continuous and remittent

TABLE 4—*Tabulation of Essential Pathologic Data of 20 Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis*

	Case																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Syphilitic aortitis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Syphilitic valvulitis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aortic insufficiency	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiac hypertrophy	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+	+	+
Other evidences of syphilis	—	—	—	—	+	—	—	+	—	0	—	0	+	0	0	0	0	0	0	0
Previous valvular changes other than syphilitic	0	0	—	0	0	0	—	0	0	0	0	0	0	0	0	0	0	0	0	0
Type of endocarditis†	S	A	S	S	A	S	S	A	A	S	A	A	S	S	S	S	S	S	S	A
Mycotic aneurysm	0	—	0	0	0	+	—	0	+	+	+	+	0	0	0	+	+	+	+	0
Myocarditis	—	—	—	—	—	—	+	0	—	0	0	0	0	0	+	+	0	0	+	0
Pericarditis	—	—	—	—	—	—	—	—	—	0	+	0	0	0	0	0	0	0	0	0
[Spleen	—	—	0	—	+	0	—	+	+	0	0	0	0	0	0	0	+	+	0	+
Infarcts Kidney	—	—	+	—	+	0	—	0	0	0	0	+	0	0	+	0	0	0	+	0
[Brain	—	—	0	—	0	0	—	0	0	0	0	0	0	0	0	0	+	+	0	0
Nephritis	—	+	—	—	—	0	—	+	—	0	0	0	+	0	+	+	0	+	0	0
Acute splenic tumor	—	—	+	+	—	0	—	+	—	0	+	+	+	0	0	+	0	+	0	0

* For a description including the location of the vegetations see the analysis of pathologic data in the text The dashes indicate lack of information

† Abbreviations indicate the type of endocarditis as subacute or acute

Laboratory Data—The urine was clear and amber colored, and the specific gravity was 1.028. It had an acid reaction and contained albumin (1 plus) but no sugar, occasional white cells and granular casts were seen. The Fishberg concentration test (unsatisfactory) showed a fixed specific gravity at 1.015. The phenolsulfonphthalein test showed 60 per cent excretion. Examination of the blood revealed 3,400,000 red cells and 12,000 white cells. The hemoglobin content was 60 per cent and the differential smear normal. Blood cultures were not made. The Wassermann reaction of the blood was positive. The Wassermann reaction of the cerebrospinal fluid was positive. The colloidal mastic curve was 3321000000. The chemistry of the blood was normal. A roentgenogram of the chest confirmed the cardiac enlargement and the congestive changes in the lungs. There was some fluid at the base of the right lung.

Clinical Course—The patient improved during the first month on being given digitalis and diuretics and being treated with general therapeutic measures. He did, however, show fluctuations of temperature of an intermittent character, the elevation never going above 101.2 F (38.4 C). On Dec. 21, 1937, he was transferred to the wards for patients with chronic conditions. At this time there were noted systolic and diastolic murmurs over the aortic region, as well as an apical systolic murmur. The patient was relatively free from edema. About six days after transfer, the temperature having been 98.4 F (36.9 C) for three days, an infection of the upper respiratory tract developed, with a mild pharyngitis, and his temperature rose to 100 F (37.8 C). Edema of the face became apparent, but there were no significant urinary changes. Generalized edema again made its appearance, and his condition gradually became more critical. For the last few days of life he was restless, dyspneic and uncooperative, and he had some blood-tinged sputum. There were never any petechiae. He died on Feb. 1, 1938, slightly more than three and one-half months after the onset of his symptoms. For the last two weeks of life his temperature was normal. Bacterial endocarditis was not suspected.

Autopsy—Anatomic Diagnosis. Examination revealed syphilitic aortitis, syphilitic valvulitis and aortic insufficiency, left ventricular hypertrophy and dilatation were present, with mural thrombi in the right auricle and generalized chronic passive congestion. There was subacute bacterial endocarditis of the aortic valve, with gram-positive cocci, possibly *Str. viridans*, and there was a small mycotic aneurysm in the right sinus of Valsalva, with a ruptured mycotic aneurysm of the right aortic cusp, healing vegetations on the aortic valve were present and an infarct in the spleen. Examination revealed an old area of encephalomalacia in the right occipital lobe, and there was scarring in the thyroid gland.

Gross Description of the Heart and Aorta. The heart was markedly hypertrophied and dilated, especially the left ventricle, and it weighed 720 Gm. There were small mural thrombi in the right auricle but nowhere else. At the root of the aorta there was typical syphilitic aortitis, with marked wrinkling and puckering of the intima and thickening of the adventitia. The breaks in the media were readily visible. This syphilitic process was directly continuous with a similar process in the sinuses of Valsalva, and from there it passed down to the aortic cusps. The aortic ring was slightly dilated. The commissures between the left and the middle cusp were thickened and fused for a distance of about 1 cm from their attachments. The left cusp had its margin displaced 6 mm below the level of the others. There was a slight fusion of the right and the middle cusps. The valve then, was obviously insufficient. The occlusal edges of the cusps were thickened and rolled. On the ventricular surfaces of the right and middle cusps there were

small yellow and white granular vegetations. This process was most extensive on the right cusp. The vegetations were in part friable, but there were also older, tough areas which were definitely organized. Some of the vegetations extended down on the endocardium of the membranous septum, but none were present along the free margins of the valve cusps. There was a small bulge at the base of the right cusp, and here there was a perforation guarded by several small vegetations.

In the sinus of Valsalva, behind the small bulge, there was a little irregular opening in the endocardium, and a small aneurysm, 5 mm deep, was found. The base of this could be seen as a yellow opaque spot in the musculature of the pulmonary conus behind the tricuspid valve. The middle cusp contained a small gray vegetation on a portion of the corpus arantii. It measured 5 mm across and was tough. The mitral valve was delicate, and its chordae tendineae showed nothing. The pulmonary and tricuspid valves were normal. The coronary arteries were delicate. In the aorta the syphilitic process extended from the sinuses of Valsalva into the ascending portion and arch. The very first part of the innominate artery was also involved by the process. The wrinkling ended at a point just beyond the subclavian artery on the left. The remainder of the aorta showed only slight changes which consisted of a few fatty streaks in the intima.

Microscopic Lesions of the Heart. The myocardium in the immediate vicinity of the aortic valve contained a small number of dense fibrous scars with a few lymphocytes about them. There was scarcely any scarring in the remaining muscle. In the right auricular appendage there were a few very slightly organized small thrombi. The mitral valve and its elastic tissue were normal. A small artery and a portion of the left circumflex artery in the sections showed no changes. There were no evidences of previous rheumatic changes.

Microscopic Lesions of the Aorta, the Aortic Valve and the Sinus of Valsalva. Several sections from different portions of the aorta all showed an advanced syphilitic process. The adventitia was thickened by dense, wavy fibrous tissue which was partly hyalinized. Many vasa vasorum and small arteries contained large collars of lymphocytes and plasma cells. Moderate numbers showed various stages of obliterative endocarditis. The media was markedly altered. There were many young stellate vascular scars with numerous lymphocytes and plasma cells about them. Numerous other dense fibrous scars caused a thinning out and many interruptions of the elastic tissue. No fresh necroses were present. The intima was irregularly thickened, was somewhat granular and showed the early changes of arteriosclerosis. It was only a little scarred. In the right sinus of Valsalva the syphilitic process was even more accentuated. There were numerous large adventitial collections of lymphocytes and plasma cells about many blood-containing capillaries and stellate scars. In the media the elastic tissue stopped abruptly at the base of the aortic valve. Here it was replaced by a dense, whorled, disordered hyaline mass in which small capillaries and focal collections of lymphocytes were embedded. The proximal portion of the valve was thickened by fibrous connective tissue in which there were numerous fibroblasts, lymphocytes and polymorphonuclear leukocytes. A little farther out the valve became hyaline and was completely perforated. From this point on, a second process of a bacterial nature was superimposed on the syphilitic lesion. The valve was distorted and heavily scarred. There were many capillaries containing red corpuscles, and the polymorphonuclear leukocytes were very numerous. At one point in the middle of the cusp the leukocytic infiltration was extremely intense, and many of the cells appeared disintegrated. Here the valve was thinner than elsewhere and somewhat necrotic, and one might suppose that this could have been the site of another

perforation Here too there were many small capillaries, almost to the point of hypercapillarization In one area the inflammatory vasculature in the valve consisted of large anastomosing and often stellate blood-containing channels, referred to by Gross and Fried⁵ in their cases of subacute bacterial endocarditis as the "spongy lesion" Beyond this point the process suddenly stopped, and the occlusal part of the cusp showed only dense fibrous tissue and was club shaped The surface of the valve in this portion contained only a small amount of hyaline material and no bacteria The endothelium of the entire valve was irregularly thickened by proliferating and inflammatory cells Attached to the endocardium of the sinus of Valsalva was a thin mass of fibrin and gram-positive cocci This vegetation lined the edges of the perforation previously mentioned and passed through it to the ventricular surface of the cusp Here the masses of bacteria were large and appeared as dense clouds Many old and previously dead cocci had lost their gram-positive staining characteristics and were now gram-negative Some of the vegetations were partially organized and capillarized At their bases they contained thin spindle-shaped fibroblasts and large oval and polygonal and mononuclear cells, with deeply staining nuclei and basophilic cytoplasm Some of the latter cells were multinucleated They were most frequently found at the bases of the organized vegetations and were reminiscent of endothelial cells or macro-

TABLE 5—Age Incidence

	Decades						
	I	II	III	IV	V	VI	VII
Acute	0	0	21 (28.6%)	3 (42.9%)	1 (14.2%)	1 (14.2%)	7 (35%)
Subacute	0	1 (7.7%)	4 (30.1%)	4 (30.1%)	3 (23.1%)	1 (7.7%)	13 (65%)
Totals	0	1 (5%)	6 (30%)	7 (35%)	4 (20%)	2 (10%)	20 (100%)

phages The presence of these cells, when coupled with the organization of the vegetations and the large number of capillaries, bespeaks a subacute rather than an acute inflammatory process Some of the fibrinous masses which were only slightly organized contained polymorphonuclear leukocytes in small clumps, and some of these in turn were necrobiotic In no instance were there heavy polymorphonuclear leukocytic infiltrations at the bases of the vegetations At most there were small numbers of lymphocytes and leukocytes, the former predominating

ANALYSIS OF CLINICAL DATA

The following analysis is based on the 11 cases collected from the literature as well as on our own 9 cases The cases will be referred to by their numbers in tables 3 and 4, our cases being 12 to 20 inclusive The age incidence is shown in table 5

From table 5 one can see that acute and subacute endocarditis occurred most frequently in early or middle adult life In the cases of the acute type the patients' ages varied from 35 years to 63 years In the cases of the subacute type the age variance was from 23 to 61 years These figures parallel those usually given for acute and subacute bacterial endocarditis, but they are too small to permit generalization The average age was higher in white than in colored patients

With both acute and subacute endocarditis the incidence was much greater in men than in women (table 6). The ratio tallies with that of uncomplicated syphilitic aortitis, but it is in contrast to the usually stated lower ratio between the sexes in the usual cases of bacterial endocarditis (1 e, 1½ 1 or 2 1).

Nine, or 45 per cent, of the patients were white, 10, or 50 per cent, were colored. In 1 case no mention of race was made. In the cases in the literature the patients were predominantly white, while in 8 of our 9 cases the patients were colored. In 1,000 consecutive routine autopsies at this hospital, 595, or 59.5 per cent, of the patients were colored and 405, or 40.5 per cent, were white. In most of the cases the patients were colored.

Type and Duration of Endocarditis—In 7 cases (35 per cent) the disease was acute and of less than one month's duration. In 13 (65 per cent) the disease was subacute. In the latter cases the shortest duration was two and a half months and the longest twelve months (table 3).

TABLE 6—*Distribution as to Sex*

	Men	Women	Totals
Acute	6 (85.7%)	1 (14.2%)	7 (35%)
Subacute	12 (92.3%)	1 (7.6%)	13 (65%)
Totals	18 (90%)	2 (10%)	20 (100%)

Serologic Examinations—The Wassermann reactions of the blood were positive in 17 cases (85 per cent). In 3 (15 per cent) the reactions were negative, but histories of antisyphilitic therapy were obtained. It is of interest to note here that several authors²⁰ have commented on the occurrence of false positive Wassermann reactions of the blood in the course of subacute bacterial endocarditis. The Wassermann reactions of the spinal fluid were positive in 5 cases, negative in 8 and not recorded in 7.

Duration of Syphilis—The duration of syphilis was known in only 10 cases. The shortest was four years (23 year old Negro man), and the longest was forty-six years (63 year old white man).

Antisyphilitic Therapy—In 8 cases (40 per cent) the patient received inadequate therapy, in 9 cases (45 per cent) the patient received none, and in 3 no mention was made concerning this point.

History of Rheumatic Fever—In 18 cases (85 per cent) the patients stated they had never had rheumatic fever, and in 2 cases this information was not recorded.

²⁰ Landau, A, and Held, J. Sur la réaction de Bordet-Wassermann positive au cours de l'endocardite lente, Bull. et mém. Soc. méd. d'hôp. de Paris **49** 1322 (Oct. 16) 1925. Kaldewey, W. Ueber den Wert der Wassermann Reaktion bei Endocarditis, Deutsche med. Wchnschr. **49** 443 (April 6) 1923.

Portal of Infection—Of the 7 cases of acute endocarditis the portal of entry was known in 3 cases. It appeared to be (1) intra-venous administration by the "morphine addict" of unsterile tap water (case 8), (2) prostatic abscess (case 9) and (3) pneumococcic lobar pneumonia with septicemia (case 12). Of the 13 cases of subacute endocarditis the portal of entry was unknown in every case, and the postmortem observations were not illuminating on this point.

Manner of Onset—In the cases of the acute type symptoms of severe septicemia predominated. There was also extreme dyspnea in 4 of the 7 cases. In the cases of the subacute type the onset was similar to that in the usual cases of subacute bacterial endocarditis. In most of the cases, however, severe dyspnea appeared early and was followed on the average of two to three months later by peripheral edema and orthopnea. Therapy for cardiac failure was of no avail. Conspicuous by their absence were chills, chilly sensations and subjective sense of fever.

Type of Fever—In the cases of acute endocarditis the temperatures were more septic. In the cases of subacute endocarditis the elevations were slight and intermittent, with morning fall, evening rise and slight variations in the daily peaks. Normal temperatures were present in 3 (23 per cent) of these cases.

Petechiae—Only 1 patient with acute endocarditis had petechiae. Among those with subacute endocarditis 5 (38.6 per cent) had petechiae. This is definitely less than is found in the usual cases of subacute bacterial endocarditis.

Embolic Phenomena—Only 1 patient with acute endocarditis had Osler nodes. In those with subacute endocarditis 6 (46.1 per cent) complained of tenderness over the splenic area and of Osler nodes. In 2 of these patients evidence of cerebral embolism was present (cases 7 and 18).

Palpability of the Spleen—In 1 patient with acute endocarditis and in 5 (38 per cent) with subacute endocarditis the spleen was palpable.

Clubbed Fingers—One patient with acute endocarditis and 1 with subacute endocarditis (congenital) had hippocratic fingers.

Arthritis—In no case was there arthritis.

Occurrence of Nephritis—Three of the patients with acute endocarditis and 2 with subacute endocarditis had clinical nephritis. This represents 25 per cent of all the cases and is distinctly a lower incidence than is usually found in endocarditis.

Character of Pulse—Twelve patients (50 per cent) had a collapsing (Corrigan) pulse, and in 8 cases no mention was made of this condition.

Blood Pressure—Fifteen patients (75 per cent) had blood pressures typical of aortic insufficiency. Average pressures were systolic, 148 mm of mercury, and diastolic, 44 mm of mercury, the pulse pressure was 85 mm of mercury.

Cardiac Physical Findings—Twelve patients (60 per cent) showed predominantly left ventricular enlargement, 2 patients had small enlargements, and regarding 6 patients no mention was made of ventricular enlargement. Four patients had diastolic thrills. Seventeen (85 per cent) had to and fro murmurs which were not altered at any time during the course of the disease.

Roentgenographic Findings in the Heart—The left ventricle was enlarged in 10 (50 per cent) of the cases and normal in 3. No mention of roentgenographic findings was made in 7.

Urinary Findings—Red blood corpuscles were found in the urine of 6 (30 per cent) of all the patients. In 11 cases no blood was present, and in 3 this point was not mentioned. Albumin was found in 10 (50 per cent) of the cases.

Blood Findings—In all the cases in which the condition was acute the anemia was severe, the red blood corpuscles numbering less than 2,500,000 in 5 of the 7 cases. Polymorphonuclear leukocytosis was well pronounced in all. Of the patients in whom the condition was subacute 8 had red blood corpuscle counts of less than 4,000,000. The leukocyte counts were not excessive. Hemoglobin values varied from 42 to 88 per cent and were proportional to the red blood corpuscle counts.

Course and Termination—In the cases of acute endocarditis the symptoms of septicemia became progressively worse, with death occurring within four weeks. The aortic insufficiency did not appear to be influenced in any way by the superimposed bacterial endocarditis. The correct diagnosis was made in 1 case.

The course of the cases of subacute endocarditis was similar to that seen in usual subacute bacterial endocarditis except that cardiac failure was more prominent than is ordinarily observed. This condition was present in 11 (84.6 per cent) of the 13 cases of subacute endocarditis and greatly overshadowed the much subdued bacterial endocarditis. The correct diagnosis was made in 3 of the 13 cases.

Summary of Main Clinical Characteristics of Bacterial Endocarditis Associated with Syphilitic Aortic Valvular Insufficiency—The foregoing analysis of the clinical data showed that bacterial endocarditis may be engrafted on the aortic valves in cases of syphilitic aortic valvular insufficiency as two distinct types, acute bacterial endocarditis and subacute bacterial endocarditis. These types of endocarditis were found to be similar in most respects to those usually encountered in cases of acute

and subacute bacterial endocarditis. They do, however, present certain differences which we shall here summarize.

1 *Acute endocarditis*. There was a marked prevalence of this form of endocarditis in men, and there was positive evidence of syphilis in all cases, with absence of a history of rheumatic fever, marked dyspnea occurred at the onset of the disease, as well as typical physical changes referable to cardiovascular syphilis, roentgenographic evidence indicated that the aorta was widened and the heart enlarged to the left, there was no alteration of preexistent murmurs.

2 *Subacute endocarditis*. There was a marked prevalence in men and positive evidence of syphilis, with absence of a history of rheumatic fever in all the cases, absence of chills, chilly sensations or subjective sense of fever was typical in practically all the cases (91 per cent), progressive dyspnea was prominent early in the disease, with peripheral edema setting in about two to three months later. The incidence of petechiae (38.6 per cent) was diminished, in contrast to the usual 60 to 70 per cent, with diminution in the incidence of embolic phenomena (38.6 per cent), in contrast to the usual 85 to 90 per cent, there was absence of cerebral embolism in all but 2 cases, with reduction in the incidence of nephritis (15.3 per cent) in contrast to the usual 40 to 50 per cent, the color of the skin was not said to be altered in any of the cases, typical physical changes were referable to cardiovascular syphilis and the constancy of existing murmurs, roentgenographic evidence indicated that the aorta was widened and the heart enlarged to the left, the course was typically one of syphilitic cardiovascular involvement with signs of myocardial failure (left ventricular) predominating and the bacterial process very much subdued, the correct diagnosis was made in 3 (23 per cent) of these cases.

BACTERIOLOGIC STUDIES

We shall include here the results of studies done *intra vitam* and *post mortem*.

Acute Endocarditis.—Blood cultures (*intra vitam*) were made in 6 of the 7 cases. In cases 5 and 11, 2 cultures were made for each patient, but no growths were observed. From the blood obtained in case 2 a nonhemolytic streptococcus was grown on three separate occasions. In case 9, a blood culture made about two weeks before death showed a growth of *Staphylococcus albus* (urine cultures also yielding *Staph. albus*). In case 12 material for a blood culture taken twelve days before death yielded a pure growth of pneumococci (untyped), and eleven days later (a day before death) the spinal fluid culture also contained pneumococci. In case 8, although blood for a culture was not taken *intra vitam*, a postmortem culture of material

taken from the spleen showed a pure growth of hemolytic *Staph aureus*. In only 1 other case was material taken for a postmortem culture (case 9). This culture showed the same organisms as were present during life (*Staph albus*). In case 20 no cultures were made.

In all the cases the organisms were stained as gram-positive in the bacterial vegetations themselves. In case 12 the bacteria were lancet-shaped diplococci for the greater part. In case 8 they were grouped as clumps of cocci, while in the other cases no note as to the morphology of the bacteria was made. No cultures were made in case 20.

Table 7 shows the organisms found *intra vitam* and post mortem.

Subacute Endocarditis—In contrast to the cases in which the disease was acute and in which septicemia was obvious, blood cultures (*intra vitam*) were not made in most of the cases in which the disease was subacute. As has already been pointed out, the reason for this was that in most of the cases the correct diagnosis was not suspected during life.

TABLE 7—*Bacteriologic Studies in Acute Cases*

Organisms	Number of Cultures	Material
Nonhemolytic streptococcus (case 2)	3	Blood (<i>intra vitam</i>)
Hemolytic <i>Staph aureus</i> (case 8)	1	Spleen (post mortem)
<i>Staph albus</i> (case 9)	2	Blood (<i>intra vitam</i> , 2 weeks before death and post mortem)
<i>Pneumococcus</i> (case 12)	1	Blood (<i>intra vitam</i> , 12 weeks before death)
No growth (cases 5, 11)	2 each	Blood (<i>intra vitam</i>)
No culture (case 20)		

In 9 cases (4, 6, 10, 14, 15, 16, 17, 18 and 19) no cultures were made *intra vitam*. In 2 others, the cultures showed no growths repeatedly (case 1, negative results twice, and case 13, negative results three times). In 1 instance (case 3) a blood culture showed a growth of *Str viridans*. In 1 case (case 7) 2 cultures showed growths of "strepto-enterococcus" (also called *Str viridans* "r").

Postmortem cultures were made in 3 cases and were not made in 10. Of the 3 cases in which cultures were made, in 2 (cases 6 and 10) they showed growths of *Str viridans*, and in 1 (case 18) there was a non-hemolytic streptococcus. In case 10 there were intestinal infarcts as well as generalized peritonitis, and it was stated by the authors that *Str viridans* was recovered in pure growth from the peritoneal cavity. The blood cultures also showed a growth of this organism.

It appears, then, that in the cases in which cultures were made (*intra vitam* and post mortem) *Str viridans* was found in 4 cases (3, 6, 7 and 10), a nonhemolytic streptococcus in 1 (case 18), and no organisms were found in 2 cases (1 and 13). Table 8 summarizes the bacterial organisms observed in the cases of subacute endocarditis.

Bacteria were stained in the valvular vegetations in all the cases. The morphology of the organisms was not, however, always mentioned. In our own cases the organisms appeared as gram-positive cocci. Occasionally, chains or diploformations were noted, but most often the organisms were arranged in clumps. Frequently the cocci also stained gram-negative. This would indicate, according to the technic used,¹⁹ that numbers of the organisms which were nonviable *intra vitam* presented altered staining reactions *post mortem*. This change was noted in 6 of our 7 cases of subacute endocarditis (cases 13, 14, 16, 17, 18 and 19). The type of valvular reaction seen in all our cases of the subacute type was very reminiscent of the usual changes seen in endocarditis due to *Streptococcus viridans*, except that there was even greater tendency toward healing.

TABLE 8—*Bacteriologic Studies in Subacute Endocarditis*

Organisms	Number of Cultures	Material
<i>Str. viridans</i> (case 3)	1	Blood (<i>intra vitam</i>)
<i>Str. viridans</i> (case 6)	1	Blood and valve (<i>post mortem</i>)
<i>Streptoenterococcus</i> (case 7)		
(<i>Str. viridans</i>)	2	Blood (<i>intra vitam</i>)
<i>Str. viridans</i> (case 10)	1	Blood and peritoneal cavity (<i>post mortem</i>)
Nonhemolytic streptococcus (case 18)	1	Blood and valve (<i>post mortem</i>)
No growth in 2 cases (1 and 13)	2 and 3,	Blood (<i>intra vitam</i>)
No cultures in 6 cases	respectively	

ANALYSIS OF PATHOLOGIC DATA

For the sake of convenience the syphilitic and the bacterial changes will be separated, however, in all the cases both processes existed on the same valves. The gross and microscopic alterations will be considered together and not described in detail, since these changes have been mentioned extensively by other authors.²¹

Syphilitic Changes—Aortitis. In all the cases evidence of syphilitic aortitis was present. In 4 cases the exact distribution of the aortitis was not mentioned. The ascending aorta was involved in 16 cases, and the sinuses of Valsalva were implicated in all these cases. In 5 cases the arch of the aorta was involved. In 4 cases the entire aorta was affected. In 2 cases there were syphilitic aneurysms, in the sinus of Valsalva (case 5) and in the ascending aorta (case 6). In no instance were vegetations implanted on the aorta itself.

There did not appear to be any correlation between the degree or the extent of the aortitis and the size or extent of the bacterial vegetations.

Valvulitis. Evidence of valvulitis was present in all the cases. In case 16, the syphilitic process was stated as extending into the sinuses of Valsalva. The commissures were widened, and where there were no

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vegetations the thick, cordlike occlusal margins and retraction of the cusps were apparent

Aortic Valvular Insufficiency All the valves were described as being insufficient. We realize that bacterial endocarditis itself could have accounted for some of the valvular insufficiency. In an attempt to correlate the sizes of the bacterial vegetations with the degree of insufficiency it was noted that in most of the cases in which the cardiac weights were mentioned the sizes of the bacterial vegetations were inversely proportional to the sizes of the hearts. This would be another point in favor of preexisting valvular insufficiency, since usually in the absence of other causes one finds large vegetations destroying the valve leaflets in the cases of endocarditis associated with valvular insufficiency.

Cardiac Hypertrophy The heart was enlarged in 18 cases. The average weight was 645 Gm. A comparison of these cardiac weights with those found in our cases of subacute endocarditis superimposed on rheumatic aortic valves revealed that in the latter there was less hypertrophy, the average weight being 500 Gm. This, we feel, represents a significant difference.

Other Evidence of Syphilis Other syphilitic anatomic changes were evident in 3 cases: *tabes dorsalis* (case 5), possible meningitis (case 8) and orchitis (case 13).

Changes Due to Bacterial Endocarditis—**Type of Endocarditis** In 7 cases (35 per cent) the disease was acute, and in 13 cases (65 per cent) it was subacute.

Location of Vegetations In all the cases the primary vegetations were located on the aortic valve cusps. There was no essential difference between the locations of the vegetations in the cases of both acute and subacute endocarditis, hence they are considered together.

In 5 cases all the aortic cusps were involved (4 of these being of the subacute type). The individual cusps were affected in the following manner: left cusp, 8 cases, right cusp, 8 cases, and the cusp not associated with a coronary orifice, 11 cases. The sinuses of Valsalva were involved in 3 cases and the left ventricular surface of the membranous septum in 4.

One other observation is noteworthy. In 8 of our own 9 cases, the vegetations were not on the occlusal margins of the valve cusps but rather on the ventricular surfaces and bases of the leaflets (figs 1 and 5). There was no tendency for the vegetations to grow around the margins of the cusps and thus involve both sides. These features are distinctly in contrast to those in the usual form of subacute bacterial endocarditis, in which the vegetations (even rheumatic verrucae) are practically always found along the occlusal margins of the valve leaflets on both sides. The significance of these facts will be considered when the pathogenesis is discussed. In the cases taken from the literature no

mention concerning these points was found. Contact vegetations were present on the aortic surface of the anterior mitral leaflet in 8 cases; on the chordae tendineae in 4 cases and in the left auricle in 2 cases. In none of the cases were any of the vegetations implanted on the syphilitic process in the aorta.

Description of Vegetations. In 3 of the cases of acute endocarditis the vegetations were described as being large or bulky, friable, wartlike

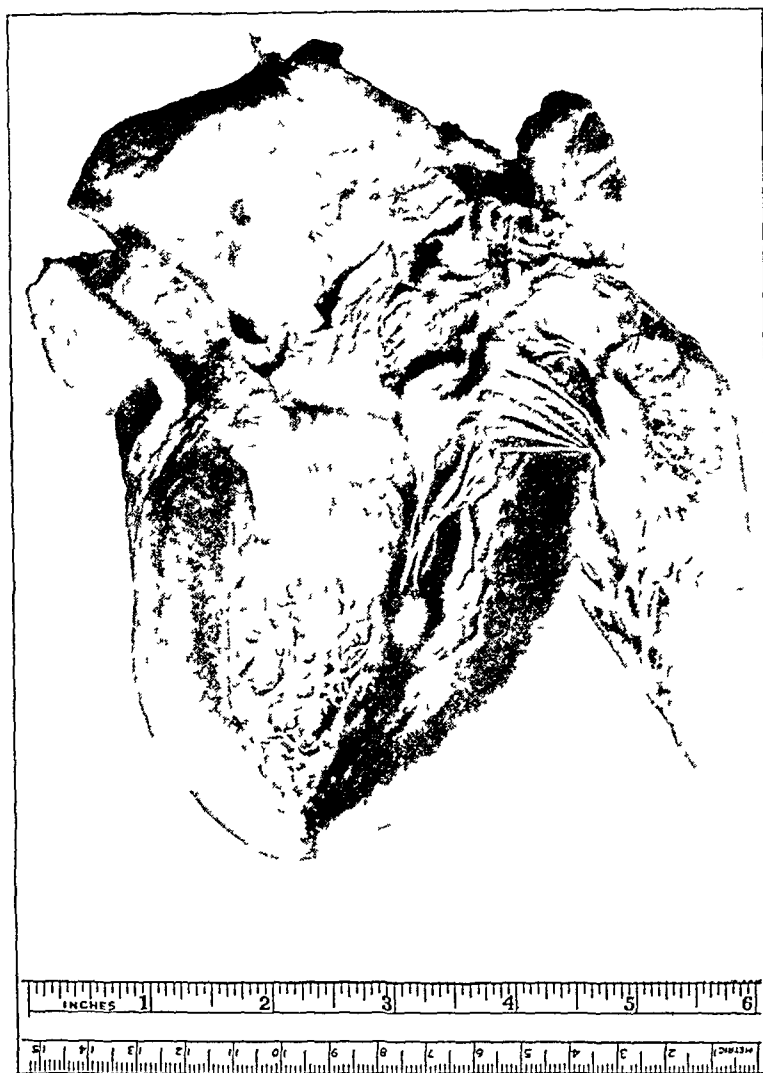


Fig 1—Heart in case 15, with syphilitic aortitis, valvulitis and large vegetations at bases and over ventricular surfaces of posterior and left aortic cusps. The thickened chordae tendineae show small stringy vegetations.

or sessile and gray or dark red. In the 3 remaining cases of acute endocarditis they were stated as being small, granular or flat, friable, yellow or yellow-gray and necrotic. Only 3 microscopic notes were recorded in the cases of this type, and these agreed completely with the usual descriptions of acute endocarditis.

In 10 cases of subacute endocarditis (77 per cent) the vegetations were small instead of being predominantly large, bulky and irregular,

as are the vegetations in most of the usual cases of subacute endocarditis. In only 2 cases (7 and 15) were there large "voluminous or polypoid" vegetations. The sizes of the others varied from "thin, granular layers" to layers 5 or 6 mm in diameter. In 7 cases the vegetations were described as being numerous, and in 6 they were localized to only one of the aortic cusps. The amount of organization did not always receive



Fig 2—Photomicrograph of a section of aorta in case 15, showing numerous stellate and vascular medial scars with scattered inflammatory cells. In the lower part of the photograph a tiny vessel is completely obliterated and partially surrounded by a cuff of lymphocytes and plasma cells. A larger, adjacent artery is almost completely occluded by an obliterative endarteritis. Hematoxylin and eosin stain, $\times 46$.

comment. In 7 of our 9 cases of the subacute type the bases of the vegetations were said to be tough and organized, while their surfaces were fairly friable. In 4 of the other cases the vegetations were stated as being partly organized or else just "friable." The colors of the



Fig 3—Photomicrograph of a section through the base of an aortic cusp showing vegetation in case 15. On the right side of the photograph the valve is scarred by dense hyaline tissue. In the body of the valve there are very numerous small blood channels, as well as large numbers of inflammatory cells. The left side of the photograph shows a portion of the bacterial vegetation with destruction of the subjacent part of the valve. Hematoxylin and eosin stain, $\times 91$.

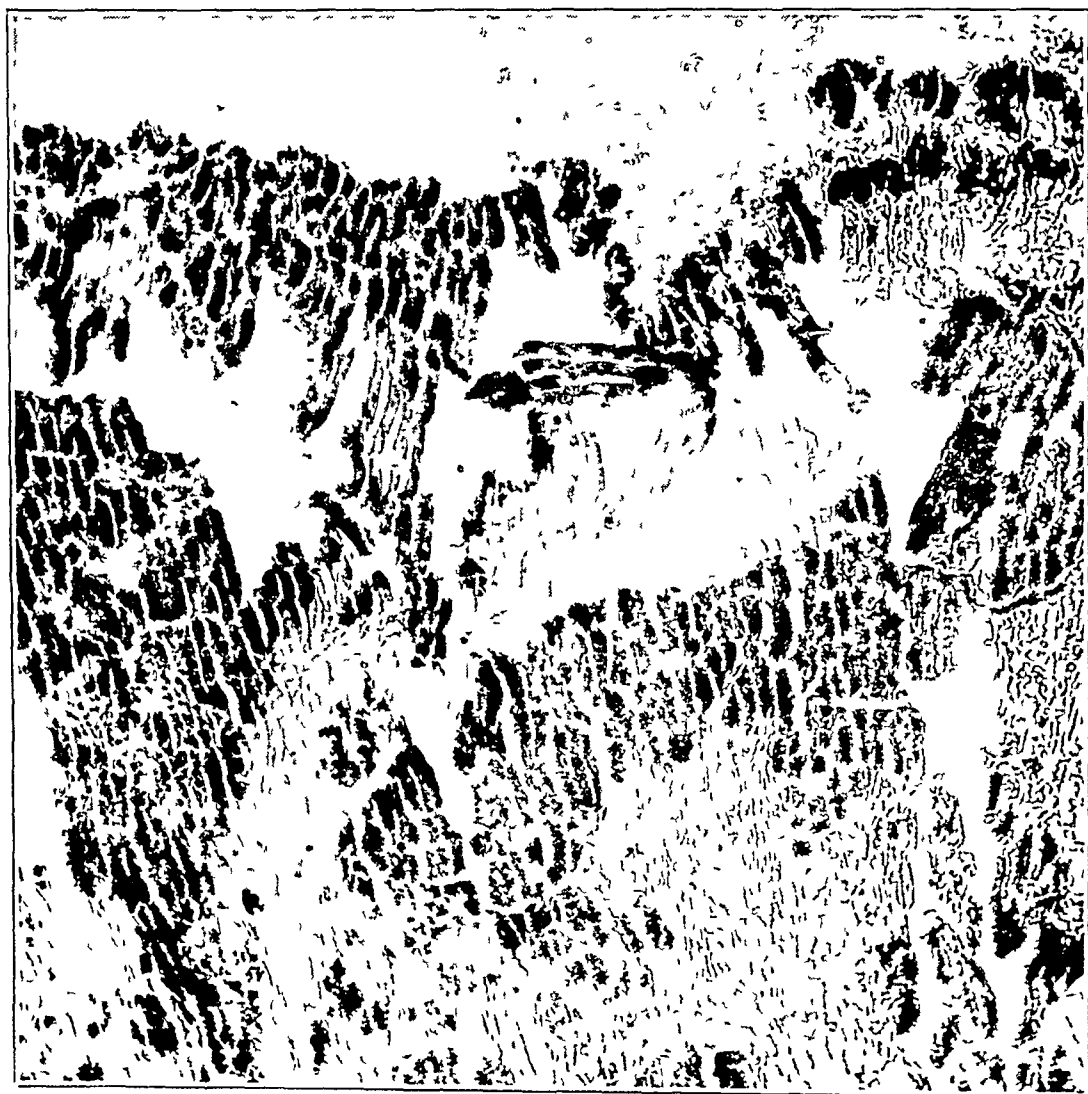


Fig 4—Photomicrograph of bacterial vegetations in case 15. The numerous black areas represent solid clumps of gram-positive cocci. Brown and Brenn bacterial stain, $\times 46$.

vegetations varied from pink, yellow, gray, and white to brownish yellow. In our own cases the aortic valve cusps were never stated as being extensively destroyed or distorted. The lack of these changes is again in contrast to the majority of the usual cases of endocarditis, in which such alterations are quite frequently described.

Microscopically, the condition in our cases was typical of the type of endocarditis seen in infections caused by *Str. viridans*, with the exception that in most instances there was distinctly more organization of the bases than is usually seen, and in the depths of the vegetations nonviable organisms were relatively more frequent. Microscopic descriptions were vague and lacking in most of the cases abstracted from the literature.

Mycotic Aneurysms in Valve Leaflets Among the cases of the acute type there were 4 aneurysms: 2 in the right aortic cusp and 1 in each of the other two cusps. There was also 1 aneurysm each in the anterior mitral leaflet and the right sinus of Valsalva. Two of the aneurysms were ruptured.

Among the cases of the subacute type there were 6 mycotic aneurysms affecting the aortic cusps: 2 in the right aortic cusp and 2 in each of the other 2 cusps. The anterior and posterior mitral leaflets and membranous septum also showed 1 aneurysm each. Five of the aneurysms in this group were ruptured. In our cases the mycotic aortic valvular aneurysms were ruptured at the bases of the cusps.

Embolie aneurysms were not mentioned in any of the cases.

Myocarditis. Among the cases of the subacute type focal areas of acute myocarditis were noted in 3 cases (15, 16 and 19). In case 7 there were "Bracht-Wachter" lesions. In 9 cases there was no evidence of myocarditis, and in 7 no description was given. There was no evidence of rheumatism in any of the cases.

Pericarditis. In case 11 only was there subacute fibrinous pericarditis. This change was absent in all of our cases and not mentioned in the remaining cases.

Embolie Phenomena. In 5 of the cases of the acute type there were septic infarcts, in 4 cases the infarcts were splenic, in 1 the infarct was renal, and in 1 case both splenic and renal infarcts were present.

In the cases of the subacute type embolic phenomena were distinctly reduced in number. In 5 cases there were evidences of emboli. In cases 17 and 18 there were splenic infarcts and old areas of encephalomalacia, in cases 3, 15 and 19 there were renal infarcts. In case 10 there was an embolus in the superior mesenteric artery, and there was widespread infarction in the patient's bowel. In 4 other cases there were no evidences of embolic phenomena, and in 3 this point was not mentioned.

Nephritis. In the cases of acute endocarditis there were 2 cases in which the patients had glomerulonephritis, in case 2 the condition was



Fig 5—Heart in case 17, with syphilitic aortitis, and valvulitis with valves displaced at different levels (aortic insufficiency) Small bacterial vegetations are present on the ventricular surfaces of right and posterior cusps Note probe passing through ruptured mycotic aneurysm at the base of right cusp



Fig 6—Photomicrograph of a section through base of ruptured mycotic aneurysm and right aortic cusp in case 17 Note vegetative material lining edges of perforation, as well as heavy inflammatory reaction beneath vegetations The more distal portion of the valve is heavily scarred Hematoxylin and eosin stain, $\times 30$

acute and in case 8 it was subacute. In 3 cases nephritis was absent, and in 2 no mention was made concerning this point.

In the cases of subacute endocarditis there were only 4 patients who had subacute glomerulonephritis (cases 13, 15, 16 and 18). No bacteria or minute emboli could be found in the kidneys of our cases. Arteriosclerotic nephritis was present in case 14. In 5 cases there was no nephritis, and in 3 this point was not mentioned. The incidence of



Fig 7—Photomicrograph of a section of aorta in case 17, showing syphilitic aortitis. White areas surrounded by the black represent medial interruptions and scars. The thick adventitia shows one small vessel with moderately advanced changes of an obliterative endarteritis. Verhoeff and Van Gieson elastic tissue stain, $\times 60$.

nephritis at autopsy, then, was distinctly less than is found in the usual cases of subacute endocarditis.

Acute Splenic Tumor. In 3 cases of acute endocarditis (cases 8, 11 and 12) acute splenic tumors were noted, and in 1 case no such tumor was observed. In the other 3 cases no mention of this point was made.

In 5 cases of subacute endocarditis (cases 3, 4, 13, 16 and 18) acute splenic tumor was observed. In 6 cases none were observed, and in 2 cases no mention was made of this point.

Meningitis. Pneumococcic meningitis occurred in case 12, a case of acute endocarditis, and the exact type of organism was unknown.

Previous Valvular Changes Other Than Syphilitic. In 18 of the cases no other valvular lesions were present. In 2 cases there was no reference to this point.

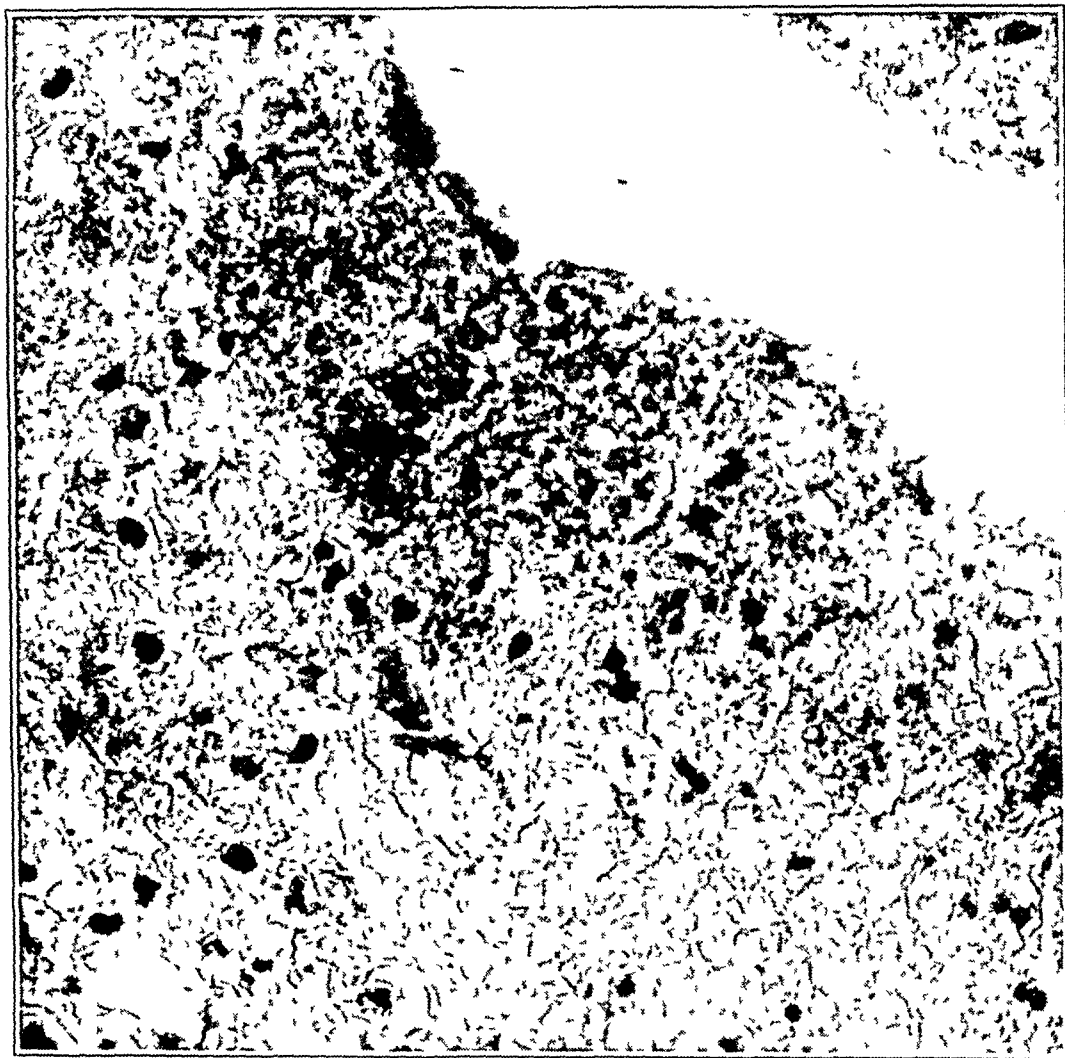


Fig 8—Photomicrograph of a section of right aortic cusp from case 6 showing vegetations containing gram-positive cocci in clumps, diplo formation and chains. The larger black areas represent nuclei of inflammatory cells. Brown and Brenn bacterial stain, $\times 1000$.

Other Postmortem Observations. In 8 cases (40 per cent of the entire series), there was generalized chronic passive congestion, and in 2 cases anasarca was present. In 1 case there was pulmonary edema. In each of 2 cases (case 12, acute endocarditis, and case 7, subacute endocarditis), there were intimal abscesses in the aorta in the vicinity of the vegetations.

Summary of Main Pathologic Characteristics of Bacterial Vegetative Endocarditis Superimposed on Syphilitic Aortic Valvulitis—At post-mortem examination, two types of bacterial endocarditis were found superimposed on syphilitic aortic valvulitis, acute endocarditis and subacute endocarditis. In 4 of the cases of the subacute type cultures made either intra vitam or post mortem showed growths of *Str viridans*. In none of the cases were there any lesions resembling those seen in association with rheumatic fever. These observations as well as those of other authors²² are decidedly opposed to the old hypothesis that rheumatic valvulitis and subacute bacterial endocarditis due to *Str viridans* are one and the same disease²³. The majority of the observations made at autopsy were similar to those of the usual forms of bacterial endocarditis. The noteworthy differences are summarized below.

- 1 Syphilitic aortitis, valvulitis and aortic insufficiency were present in all of the cases. There was no evidence of rheumatism in any of the cases.
- 2 Cardiac hypertrophy was fairly pronounced in most of the cases, the average cardiac weight in this group being greater than in our rheumatic group, in which subacute bacterial endocarditis was superimposed on the aortic valves, on the mitral leaflets or on both.
- 3 Of the cases in which the exact locations of the aortic valvular vegetations were mentioned, the majority were exclusively confined to the ventricular surfaces and bases of the cusps with no tendency to involve either the occlusal margins or the opposite surfaces of the valve leaflets. In all of our cases rupture of mycotic aneurysms occurred at the bases of the cusps.
- 4 Distortion or destruction of the aortic valve cusps was not mentioned in any of the cases.
- 5 The sizes of the vegetations were just the reverse of what is found in the usual cases of bacterial endocarditis. In the cases of acute endocarditis most of the vegetations were described as being large. In the cases of subacute endocarditis the vegetations were small in the majority of instances. In our cases, also, the bases of these vegetations were more organized than usual and frequently contained gram-negative (nonviable) bacteria.
- 6 The incidence of embolic phenomena and nephritis was distinctly reduced in the cases of subacute endocarditis.

22 (a) Koester, K. Die embolische Endocarditis, *Virchows Arch f path Anat* **72** 257, 1878. (b) Grant, R. T., Wood, J. E., Jr., and Jones, T. D. Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis, *Heart* **14** 247 (Aug.) 1928. (c) Nedzel, A. Experimental Endocarditis, *Arch Path* **24** 143 (Aug.) 1937. (d) Thayer.³

23 Sprague, H. B. Subacute Bacterial Endocarditis, *J. A. M. A.* **94** 1037 (April 5) 1930. Levine.⁶

COMMENT

In the introductory remarks it was indicated that the occurrence of bacterial endocarditis engrafted on syphilitic aortic valves was regarded as rare. It was also intimated that one possible reason for this, in the more or less universal opinion of the investigators, was that the earlier recognition of rheumatic valvular disease and its association with bacterial endocarditis (especially the subacute variety) caused most observers to focus their attention almost exclusively on the relationship between these two pathologic entities. Consequently, many authors have stressed the point that previous rheumatic valvular lesions are prerequisite for the occurrence in most cases of bacterial endocarditis.³ When one examines the analyses of a series of cases of endocarditis, however, frequently only the figures on the percentile occurrence on previously damaged rheumatic valves is given. These figures almost always vary from 60 to 80 per cent. What, then, is the basis for the occurrence of the disease in the remaining 20 to 40 per cent? Bicuspid normal and arteriosclerotic valves sometimes account for the remainder,²⁴ but most frequently no stated analyses are presented. Our own observations would indicate, moreover, that the combination of bacterial endocarditis and syphilitic aortic valvulitis is more common than is generally stated, and thus we are reasonably certain that further study of cases of endocarditis would reveal relatively more cases similar to the ones analyzed. This would be especially true of conditions occurring in regions where endocarditis and syphilis exist side by side. It is realized, however, that from the *absolute* point of view this combination of maladies is not nearly as common as the occurrence of bacterial endocarditis on valves previously altered by rheumatism, hence other explanations for this infrequency must be sought.

The pathogenesis of bacterial endocarditis has often been discussed.²² Among the possible mechanisms that lead to the valvular implantation of bacteria, the hemodynamic factor of tension seems especially pertinent in this group of cases. It has already been pointed out⁵ that the "formation of rheumatic verrucae in rheumatic cardiac disease is considerably influenced by mechanical stress and strain" and "the closure lines of those valve leaflets that are subjected to the greatest pressure changes (left ventricle) become the seat of verrucous formation." It has also been observed that in cases in which the valves "have become so stiffened that they cannot close, a new line of verrucae forms on the site most exposed to eddies and blood currents." More recently Nedzel^{22c} has concluded from his experimental work that "pressor episodes" may play a role in the valvular preparation for bacterial implantation (adhesiveness), as well as in the causation of bacteremia. Furthermore, in a

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variety of conditions⁵ proliferative lesions (eosinophilic multinucleated inclusion bodies) are formed along the occlusal margins of the valves and may form a suitable site for anchorage of bacteria. These changes are stated to be more frequent on rheumatic valves than on normal ones. The mechanism for the formation of bacterial endocarditis on normal valves is the same as in the rheumatic. The components, however, are reduced in number, and herein lies at least a partial explanation for the reduced incidence of endocarditis on such valves.

Further evidence that the hemodynamic factors are intimately concerned in the causation and localization of bacterial vegetations is to be found in the examples of severe mitral stenosis. Such instances of "stiffened valves" have already been referred to, and superimposed bacterial endocarditis on valves so affected is extremely uncommon.²³ It might also be pointed out that in cases of chorea bacterial endocarditis is uncommon, while mitral stenosis is relatively frequent. Again, the incidence of rheumatic valvular disease in general and mitral stenosis in particular is greater in women, but the incidence of bacterial endocarditis is greater in men.⁶ Among our own cases of rheumatism it has been found that in patients with advanced aortic insufficiency bacterial endocarditis was also very uncommon. Most of the cases of rheumatism with aortic bacterial endocarditis have been regarded by us as instances in which the altered valvular margins were still completely or partially capable of opposing each other. Moreover, the vegetations were primarily on the occlusal margins in these cases. It is also felt that if rheumatic aortic valvular insufficiency comparable to that associated with syphilitic valvulitis were present before the onset of bacterial endocarditis, cardiac hypertrophy should be greater in the former because of the added extensive destruction of the valve cusps. But, as a matter of fact, the average cardiac weights were less in the cases of rheumatism with bacterial endocarditis than in the cases of syphilis. The marked evidences of insufficiency observed in these cases, then, represent the effects of destruction of the valve cusps, in contrast to the almost uniform lack of such alterations in the cases of syphilitic aortic insufficiency.

When one comes to a consideration of the cases of syphilis, it becomes apparent that certain of the aforementioned predisposing factors suitable to the formation of endocarditis are absent. The valve cusps cannot approximate each other and consequently are unable to cause irritation of their scarred occlusal margins. Hence, they form a relatively poor anchoring ground for bacteria and vegetations. This, of course, is distinctly in contrast to what has been said about the rheumatic valves. The fact that in cases of syphilis the greatest tension and irritation are exerted on the ventricular surfaces and bases of the cusps explains most

satisfactorily the localization of the vegetations on the latter areas in most of our own cases. It would also account for the fact that the vegetations were small and showed marked tendency toward healing, because of less friction than is found between opposing lines of closure. In connection with these observations, it might be mentioned that bactericidal agents could conceivably be more efficacious than usual in the treatment of endocarditis in syphilitic patients, in view of the great natural tendency of the vegetations to heal.

The clinical and pathologic differences from the usual forms of subacute bacterial endocarditis have already been outlined. These departures from the usual forms of subacute endocarditis are explained by the alterations in pathologic findings as well. Thus, with the evidences of greater healing and smaller vegetations, the lessened incidence of petechiae, embolic phenomena and nephritis, as well as the very low grade sepsis can be explained. The lack of valvular destruction and the presence of small vegetations in most of the cases account for the constancy of the murmurs. The sepsis, though milder than usual, is enough to cause the moderate anemia and the general debility which the patients experience. The progressive cardiac failure with dyspnea and orthopnea is then to be expected in view of the extra load thrown on the already overburdened heart.

SUMMARY

The clinical and pathologic observations in 20 cases of bacterial endocarditis superimposed on syphilitic aortic valvulitis have been analyzed. Two types of endocarditis exist, acute and subacute. Both, though similar to the usual types of endocarditis, do present certain differences.

In cases of the acute type there was a marked prevalence in men, in all the cases of this type there was positive evidence of syphilis and absence of a history of rheumatic fever, marked dyspnea was present at the onset of the illness, and there were typical signs of syphilitic aortic valvular insufficiency and septicemia. At autopsy the aortic valvular vegetations were described as large in most of the cases in which the size was mentioned. There were syphilitic aortitis, valvulitis, aortic insufficiency and cardiac hypertrophy in all. No changes due to rheumatic fever were present in any cases.

In the cases of the subacute type there was also a marked prevalence in men, and there was positive evidence of syphilis and absence of a history of rheumatic fever in all the cases in which this point was mentioned, no chills, chilly sensations or subjective sense of fever were reported in most of the cases, there was progressive dyspnea early in the disease, with peripheral edema setting in about two months later, reduced incidence of petechiae, embolic phenomena and nephritis, there

were no changes in the color of the skin of the white patients, typical syphilitic aortic valvular insufficiency was present, and the course was typically one of cardiovascular syphilis with signs of myocardial failure (left ventricular) predominating and endocarditis appearing subdued. Postmortem examinations revealed syphilitic aortitis, valvulitis and aortic insufficiency in all the cases, cardiac hypertrophy was pronounced, the average cardiac weight being greater than in the cases of rheumatism with aortic valvular bacterial endocarditis. In our cases the vegetations were noted on the *ventricular surfaces and bases* of the valves and not on the occlusal margins, the vegetations were small, with a marked tendency toward healing, destruction or distortion of the aortic cusps was not mentioned in any case, there was no evidence of rheumatic changes in any of the cases (1 e, in the valves and myocardium).

From the analysis of the bacteriologic studies it was found that in most of the cases acute endocarditis was caused by pyogenic organisms. In 1 case it was caused by a nonhemolytic streptococcus. In 2 cases materials taken for cultures repeatedly showed no growths, and in 1 case no cultures were made.

In the cases of subacute endocarditis *Str. viridans* was observed in materials taken for culture *intra vitam* in 2 cases and post mortem in 2 cases. A nonhemolytic streptococcus was observed in materials taken for culture post mortem in 1 case. In 2 cases cultures (*intra vitam*) repeatedly gave negative results, and in 6 instances no material was taken for culture.

The diagnosis of the simultaneous presence of both conditions is admittedly difficult, since not many clues are present to arouse suspicions of the existence of bacterial endocarditis. Aortic insufficiency will in most instances be readily perceived. Subacute endocarditis, however, will in most of the cases manifest itself only by a gradual progressive anemia, associated with slight daily intermittent rises in temperature, to 100 or 101 F. Without other explanation for these conditions (fever and anemia) bacterial endocarditis superimposed on syphilitic aortic valvulitis must be suspected, and blood cultures should be made repeatedly if negative results are given. (In practically all of our cases the temperature elevation was thought to be due to terminal pneumonia, while the anemia, in most instances, was ignored.)

When the evidences of subacute endocarditis are more outspoken (1 e, embolic phenomena, petechiae and nephritis), then the diagnosis becomes simpler, but it must be remembered that these frank forms of subacute bacterial endocarditis are only occasionally (as far as we could make out) implanted on syphilitic aortic valves. Most frequently they are located on rheumatic or normal valves, and the occurrence in these cases of positive Wassermann reactions would tend to throw one

off the right track. In the presence of definite syphilitic aortic insufficiency, bacterial endocarditis, if obvious, is most likely to be situated on a valve other than the aortic. This will probably be true in most cases, even though it may be known that syphilitic aortic insufficiency has existed for a long time before the present illness

SUMMARY AND CONCLUSIONS

The clinicopathologic observations of bacterial endocarditis (acute and subacute) superimposed on syphilitic aortic valvulitis are presented in detail

To the 11 cases found in the literature, 9 of our own have been added, the total of 20 "proved" cases including 7 of acute and 13 of subacute endocarditis

That the diagnosis may be concomitant existence of the two conditions may be suspected when in the presence of syphilitic aortic valvular insufficiency a gradually progressive anemia exists with slight daily intermittent rises in temperature which cannot be explained by any other observations. Frank evidence of bacterial endocarditis in the presence of syphilitic aortic insufficiency usually bespeaks the involvement of a valve other than the aortic

The pathogenesis of bacterial endocarditis is discussed in relation to our 9 cases, and possible reasons for the infrequency of the simultaneous occurrence of syphilitic aortic valvulitis and bacterial endocarditis are presented

Dr Frank B Kindell and Dr John T King Jr aided in the preparation of this paper

FURTHER EXPERIENCE WITH THE ROENTGEN DIAGNOSIS OF IDIOPATHIC STEATORRHEA

REPORT OF CASES, INCLUDING POSTMORTEM OBSERVATIONS
IN ONE CASE

JOHN L KANTOR, M D
NEW YORK

In a recent paper ¹ I reported 6 cases of so-called idiopathic steatorrhea, including roentgen examinations. The diagnosis of this symptom complex, which includes nontropical sprue, intestinal infantilism and celiac disease, was based on the following considerations: (1) Steatorrhea was demonstrated in each instance, (2) in the few cases in which the fat partition in the stools was determined, it was normal, (3) examination of the duodenal ferments in 1 case gave normal values, (4) in no instance up to the time of publication of the paper was there any clinical evidence of pancreatic involvement. In addition, in the 6 cases there were other clinical features generally assumed to accompany idiopathic steatorrhea, namely, anemia, flat blood sugar curve, tetany and low serum calcium. However, not all of these features were present in all the cases, nor were the features always constant in the same case.

Roentgenologically, there were noted changes in the bones, faint filling of the gallbladder, ileal stasis and colonic dilatation and redundancy, and, most striking of all, in 4 cases there was the peculiar smooth appearance of the upper part of the small intestine which I have described as the "moulage sign." This appearance was first reported by Snell and Camp,² in 1934. In 1 case there was, in addition to the "moulage" appearance, an intermittent dilatation with spasm in the loops of the small intestine, a phenomenon which had been previously described by Mackie, Miller and Rhoads,³ in 1935. These findings were sufficiently distinctive to enable me to make a diagnosis of idiopathic steatorrhea on inspection of the roentgen films alone. In a recent conversation I learned that Dr. Walter C. Alvarez has had the same experience.

1 Kantor, J. L. The Roentgen Diagnosis of Idiopathic Steatorrhea and Allied Conditions. Practical Value of the "Moulage Sign," *Am J Roentgenol* **41** 758-779, 1939.

2 Snell, A. M., and Camp, J. D. Chronic Idiopathic Steatorrhea. Roentgenologic Observations, *Arch Int Med* **53** 615-629 (April) 1934.

3 Mackie, T. T., Miller, D. K., and Rhoads, C. P. Sprue. Roentgenologic Changes in the Small Intestine, *Am J Trop Med* **15** 571-590, 1935.

Since writing the original paper I have observed 2 new cases, 1 of which I have had the opportunity of following to autopsy. In this instance it was possible to demonstrate complete loss of intestinal valvulae in the areas where the "moulage sign" had been observed, the anatomic basis of the sign was thus established. It is the plan of this paper to recapitulate briefly the 6 cases already reported, noting new developments where these have occurred, and then to report in detail the new material.

CASES PREVIOUSLY REPORTED

CASE 1—The patient was a woman aged 45 with a history of probable steatorrhea in childhood. There was marked dwarfing of the skeleton, with deformity of the bones and osteoporosis. During an "active period" observation at Montefiore Hospital showed steatorrhea, abdominal distention and a flat blood sugar curve. The "moulage sign" was not demonstrated.

CASE 2—A woman 55 years old gave a history of long-standing duodenal ulcer and of a ten year period of unexplained loss of weight, which had terminated in a recent phase of frothy diarrhea with marked abdominal distention. Death ensued from perforation of, and hemorrhage from, the ulcer. The combination of peptic ulcer with steatorrhea has been previously described in the literature and will be mentioned again in case 7. A "moulage sign" was demonstrated. The gallbladder was not studied.

CASE 3—A man of 30 suffered from marked malnutrition, with loss of almost half his normal body weight, achlorhydria, gastrosplasm and pylorospasm, which led to exploratory laparotomy and gastrotomy, anemia, psychotic symptoms, tachycardia, hyperhidrosis, and asthenia. There were colonic dilatation and redundancy. The "moulage sign" was not demonstrated. The gallbladder was not studied. Through Dr. J. S. Diamond⁴ it was learned that a subsequent study of the pancreatic secretion by the new secretin technic showed a diminution in the concentration of lipase to 32 units, as against a normal minimum of 153 units. Thus there is a possibility that this case may, after all, be one of pancreatic insufficiency rather than one of idiopathic steatorrhea. It should be observed in this connection that up to the present time it has been impossible to set definite quantitative limits for normal values for lipase, presumably because most of the studies reported were done on the mixed duodenal secretions (Comfort, Parker and Osterberg⁵) instead of on the pure pancreatic juice obtained by the new technic⁶.

4 Diamond, J. S.; Siegel, S. A.; Gall, M. B., and Karlen, S. The Use of Secretin as a Clinical Test of Pancreatic Function, *Am J Digest Dis* 6:366-372, 1939.

5 Comfort, M. W., Parker, R. L., and Osterberg, A. E. The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen, *Am J Digest Dis* 6:249-254, 1939.

6 Ågren, G., and Lagerlof, H. The Pancreatic Secretion in Man After Intravenous Administration of Secretin, *Acta med Scandinav* 90:1-29, 1936. Ågren, G., Lagerlof, H., and Berglund, H. The Secretin Test of Pancreatic Function in the Diagnosis of Pancreatic Disease, *ibid* 90:224-271, 1936. Chiray, M., and Bolgert, M. Le test à la sécrétine dans les affections du pancréas, *Arch d mal de l'app digestif* 29:5-32, 1939. Diamond, Siegel, Gall and Karlen⁴.

CASE 4—A woman aged 45 suffered from steatorrhea complicated by severe abdominal pain, hemorrhagic diathesis, anemia, tetany, amenorrhea, disturbed water metabolism, transient severe leukocytosis and increased coagulation time. Roentgen studies showed colonic dilatation and a "moulage sign" which persisted for over a year before appropriate therapy was instituted. After treatment for sprue the "moulage sign" diminished and there was clinical recovery. The gallbladder was atonic and filled faintly at the original examination. Hemorrhage into the digestive tract took place, this was unusual, but it had been previously reported in the literature by Holst⁷ and Snell⁸ and was again observed in case 7.

After the steatorrhea was controlled, pain developed in the left upper quadrant of the abdomen, which always came on in the late afternoon, evening or night. Pain is not usual in idiopathic steatorrhea but was observed again in case 7. Belladonna, alkalis and calcium had some effect on the pain, but the most reliable medicament was acetylsalicylic acid. Since the salicylates are known to be cholagogues this observation is interesting. After the original examination bile salts were administered for one month. The gallbladder was then restudied, it was found to be smaller in size, and the concentration of dye was greater.

CASE 5—A woman aged 27 suffered from fatty diarrhea and malnutrition. Hypochromic anemia, which changed to a hyperchromic form during treatment, a low blood calcium and a typical flat blood sugar curve were found. The "moulage sign" was present for at least three years before specific treatment was started, but it practically disappeared after a month of management for sprue. Roentgenologic study of the gallbladder showed faint filling with dye. Since the time of the original report the patient has survived an attack of pneumonia, and in April 1939 she completed a normal pregnancy and labor.

CASE 6—A single man 21 years old had steatorrhea with only mild diarrhea. The disease had been characterized by foul stools, occasional cramps and fever, intercurrent jaundice, considerable malnutrition, progressive secondary anemia, abdominal distention, sore tongue, pains in the legs, moderate osteoporosis and pigmented cutaneous lesions.

Roentgenologic examination showed a dilated colon and almost complete lack of filling of the gallbladder. The roentgen appearance of the small intestine was striking. The first two or three loops of the jejunum were normal, but the succeeding convolutions showed not only complete absence of valvulae but a remarkable segmentation, in which enormously dilated smooth segments were separated by spastic areas which caused temporary arrest in the passage of the barium sulfate.

Since the original report the patient has improved clinically to such an extent that he considers himself well. When last seen he weighed 155 pounds (70 Kg) (a gain of about 27 pounds [12 Kg] in all). Despite this clinical progress the appearance of the jejunum remained unchanged for three months after the original examination, it was not until March 13, 1939 (that is, nine months after the original observation) that a roentgen examination showed somewhat less dilatation and spasm of the upper jejunal loops. The progress of the barium through the small intestine was definitely more regular and more rapid. The stomach took four hours to empty instead of the three hours required on

7 Holst, J. E. Ein in Danemark aufgetretener Fall von Sprue, *Acta med Scandinav* 66 74-99, 1927.

8 Snell, A. M. Tropical and Nontropical Sprue (Chronic Idiopathic Steatorrhea) Their Probable Interrelationship, *Ann Int Med* 12 1632-1671, 1939.

previous occasions. In other words, there seemed to be a very gradual improvement in the pattern and function of the small intestine. This improvement, however, will need to be confirmed by further observation.

The examination of the gallbladder was repeated after eight and one-half months, and again there was almost complete lack of filling. The patient is now receiving bile salts.

NEW CASES

CASE 7—A boy 9 years old was observed in the medical service at the Montefiore Hospital from Sept 22, 1938 to Jan 5, 1939.

History—At two and one-half years of age the patient began to have two to three large stools daily. Two years later (1933) fever, abdominal distention, diarrhea and anemia were present. A clinical diagnosis of celiac disease was made about this time by Dr. Sidney V. Haas,⁹ and enlargement of the liver and spleen were noted. The patient failed to cooperate in attempts to establish a dietary regimen proper for a person with celiac disease. In July 1937 the boy was admitted to the Lebanon Hospital because of vomiting and abdominal pain. There roentgenologic examination showed marked dilatation and spasm of the duodenum and jejunum, with absence of valvulae and delayed gastric emptying. These findings were interpreted as representing a partial obstruction due to congenital bands or inflammatory adhesions, but at exploratory laparotomy, on April 14, 1938, nothing was found but dilated loops separated by areas of intense spasm. The findings were subsequently interpreted as those of "intestinal tetany." Following the operation there were hematemesis and melena, a marked anemia developed, for which the patient received fifteen blood transfusions (300 cc each) within a few months, without much improvement. At this time the boy began to present a serious behavior problem. He was noncooperative and complained of pain, for which no basis was evident and which was relieved by various procedures, including the injection of sterile water. On retrospect, however, it seems likely that the boy was actually suffering from intestinal spasm of greater or less severity and duration. At any rate, the pain never followed any special time pattern. There was no dysphagia. Unfortunately, it was never possible to impose any strict dietary regimen at any time, either in the hospital or at home.

In August 1938 the patient was admitted to Lincoln Hospital, where he was found to have dilatation of the esophagus as well as delayed gastric emptying.

On Sept 22, 1938 the boy was admitted to Montefiore Hospital with the same complaints as in 1933—namely, fever, distention, diarrhea and anemia—plus hematemesis and melena.

Physical Examination—There was much emaciation, the weight on admission being 17.7 Kg (39 pounds). The height was 118 cm (3 feet 10 inches). The abdomen was greatly distended (fig 1). The liver and spleen were palpable. There was universal adenopathy, particularly marked in the groins, axillae and neck. The abdominal distention was attributed by some persons to ascites, but the fluid was probably all intraintestinal.

Laboratory Data—On admission to the hospital the hemoglobin was 69 per cent. There were 4,710,000 red cells and 10,360 white cells, the differential count was normal. The erythrocyte sedimentation time was 10 mm in one hour. The value for blood sugar was 99 mg per hundred cubic centimeters, for urea

9 Haas, S. V. Celiac Disease. Its Specific Treatment and Cure Without Nutritional Relapse, J. A. M. A. 99:448 (Aug 6) 1932.

nitrogen, 15.1 mg, for cholesterol, 167 mg, and for cholesterol esters, 111 mg (all these values are normal). A dextrose tolerance test was not made, nor were the gastric contents analyzed after a test meal.

An estimation of the fat in the stools during the diarrhea phase showed that 24 per cent of the total fat intake was being excreted. This is almost five times the normal loss of fat, which is usually given as 5 per cent of the amount ingested. A determination of the partition of fat in the stool could not be carried out.

Roentgen Findings—Dr J. Bower studied the bones (March 18, 1938) and found that the epiphyses corresponded to those of a child between 5 and 6 years of age.

On roentgen examination of the gastrointestinal tract (Oct. 31, 1938) I found that the esophagus was dilated and showed a fluid level. All films showed gas pockets and dilatation of the distal portion of the colon.

The stomach at first emptied rapidly into the duodenum, which was dilated and completely devoid of valvulae. For about a half-hour there was an occlusive spasm just proximal to the duodenojejunal angle. The barium sulfate meal then entered the greatly dilated jejunal loops, which were entirely smooth and had a



Fig. 1 (case 7)—Photograph of patient, showing extreme emaciation, enlarged abdomen and laparotomy scar.

marked "moulage" appearance (figs. 2 and 3). The proximal loops—that is, those in the left upper quadrant—retained the barium for about one and one-half hours. During this time the patient experienced pain, which persisted for one and one-half hours despite the administration of 15 minims (0.92 cc) of tincture of belladonna and one-fifth grain (12 mg) of codeine.

Two hours after the ingestion of barium the head of the column had reached the lower jejunal loops—that is, those in the left iliac fossa. At two and one-half hours the small intestine was filled to the right of the midline, this observation suggested that the ileum was now receiving the barium. At five hours the barium had left the jejunum, despite the fact that there was still a gastric residue. At the twenty-nine hour observation a small gastric residue persisted, despite the occurrence of vomiting in the interval.

The gallbladder was not studied.

Summary of Roentgen Findings—The outstanding observations were as follows: dilatation of the esophagus, dilatation and segmentation of the duodenum and jejunum, absence of valvulae in the duodenum and jejunum ("moulage sign"), delayed gastric emptying, very irregular passage of barium through the small intestine, due to spasm.

Course—For a while diarrhea and distention persisted, but soon these disappeared simultaneously and did not return. The diarrhea consisted of three to

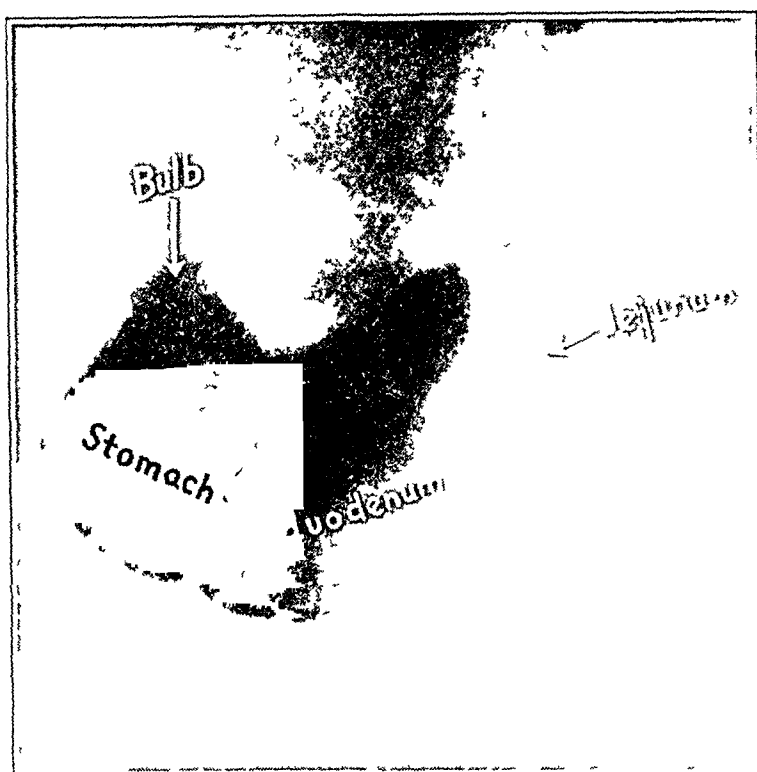


Fig 2 (case 7) —Roentgenogram taken thirty-five minutes after ingestion of a barium sulfate meal, showing dilatation of the duodenum and occlusive spasm of the proximal portion of the jejunum with the “moulage sign” (loss of valvulae conniventes) Note that the meal has not progressed beyond the first loop of the jejunum



Fig 3 (case 7) —Roentgenogram taken forty-five minutes after ingestion of a barium sulfate meal (ten minutes after figure 2), showing sudden release of the spasm with resultant filling of the next few jejunal loops Note the typical “moulage sign” and the dilatation and spasm

four copious watery stools per day, later there was one mushy stool daily. The pain became localized in the left upper quadrant of the abdomen. It was still irregular in onset, and it was difficult to understand what controlled it. However, belladonna seemed to give more relief than other forms of medication.

An attempt was made to place the child on a diet appropriate for a person with sprue, and calcium, nicotinic acid, liver extract (parenterally) and vitamins were administered. For a time the patient gained weight (3 Kg in all), but he always remained a most serious behavior problem. Much ground was lost owing to several recurrences of hematemesis and melena. The hemoglobin dropped as low as 20 per cent. Feeding was particularly difficult and ultimately required the use of an intragastric tube and the employment of special nurses. Regurgitation of food was frequent, and the weight ultimately dropped to 14.9 Kg (33 pounds). Despite all efforts the condition became worse, and the lad succumbed to inanition and exhaustion on Jan 5, 1939.

Autopsy—The autopsy was conducted by the department of pathology of Montefiore Hospital.

The liver weighed 850 Gm and measured 21 by 15 by 5 cm. Its capsule was smooth and glistening, and its color was purplish blue. On section, the surface was deep red, in some areas, particularly in the subcapsular region, the color was almost cyanotic. There was some distortion of the lobular structure, and there were numerous yellowish specks (1 to 2 mm in diameter) throughout the parenchyma. Microscopically, the liver showed marked central congestion. There were numerous foci of fatty infiltration. The central veins were dilated and engorged. Several portal areas showed small collections of lymphocytes and polymorphonuclear cells.

The gallbladder was small and of normal shape, it contained about 30 cc of golden brown bile. The bile ducts were patent and not dilated. There were no stones.

The pancreas weighed 38 Gm. On section, a normal lobular structure, with a fair amount of congestion, was noted. The pancreatic ducts were not dilated. Microscopic examination showed that the islets were small but not decreased in number. The acini were normal, the blood vessels were congested.

The spleen was grossly enlarged, it weighed 190 Gm (its normal weight in adults is 100 to 120 Gm), and it measured 14 by 8.5 by 3 cm. The capsule was glistening, and normal wrinkling was absent. On section, the surface was deep red and was fairly firm. There was an increase in fibrous stroma. The pulp did not scrape easily, and the follicles were indistinct. Microscopic examination disclosed that the lymph follicles were small and discrete, many contained fairly large cells with abundant clear-staining cytoplasm and large round clear nuclei with prominent nuclear membranes (histiocytes). The small vessels were thin walled. The pulp was congested, and there was diffuse hyaline fibrosis.

The adrenals were normal in shape but somewhat small (weight of both, 8 Gm). On multiple section, the cortex appeared to be thin. The medullary portion was normal. Microscopic examination showed marked congestion. The zona glomerulosa and the zona fasciculata were very rich in lipoids. The inner cortical zone was rich in deep brown pigment. The periadrenal adventitia was congested and contained fat droplets with a pale blue mucoid matrix (hibernating).

The thymus was not present.

The first half of the esophagus was normal, but the distal half was dilated to twice the normal diameter and at the cardiac portion its lumen was constricted to a very small opening by a thick fibrous band which was continuous with the margin of the esophageal hiatus of the diaphragm. Immediately above this

constriction there was an ulceration in the mucosa, approximately 0.5 cm in diameter. The floor of the ulcer was smooth and thickened, and the ulcer appeared to be healed. The regional lymph nodes were especially prominent. Microscopically, all layers and secretory glands were normal, there was perhaps some thickening of the skeletal muscle fibers.

The stomach was somewhat dilated. The mucosa was glistening and gray-brown. The rugae were prominent. Some pinpoint agonal hemorrhages were noted. There was an indentation at the midportion of the greater curvature of the stomach, and the omentum was drawn up at this point. Microscopic examination revealed hyperplasia of the mucous cells, numerous parietal cells and focal collections of lymphocytes, with a few plasma cells and eosinophils scattered through the tunica propria and the epithelial layer. There was congestion in the latter areas.

Examination of the small intestine showed the duodenum to be bile stained. The third portion of the duodenum and the first 2 feet (60 cm) of the jejunum

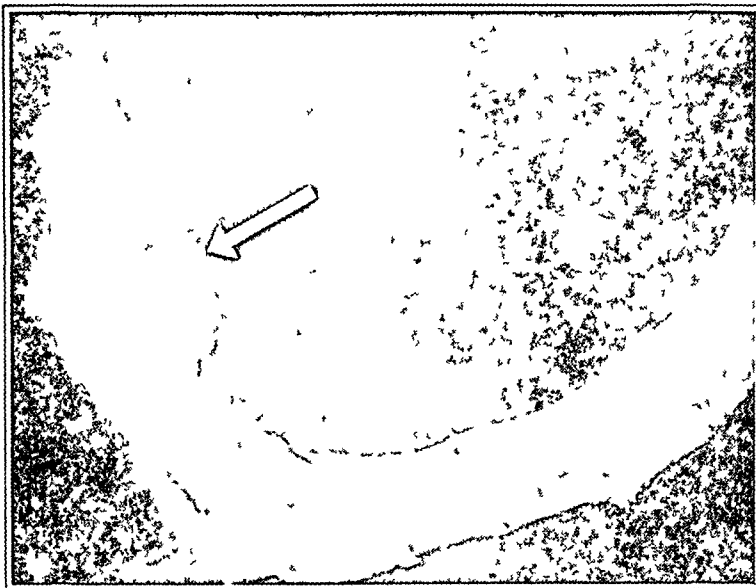


Fig 4 (case 7)—Loop of jejunum showing dilatation with complete loss of valvulae on the left except for a tuft of large coarse folds at the left center (arrow). On the right the valvulae are almost normal.

were dilated to about twice the normal diameter. The mucosa was pink-gray, but extensive areas in this portion showed complete absence of the valvulae conniventes (fig 4). The thinned areas of the jejunum were definitely pouched, and between such areas the mucosa was hypertrophic and thickened and the valvulae conniventes were accentuated. There were in this region, however, several small areas having valvulae of a peculiar circinate and serpiginous character. The distal portion of the jejunum had a normal structure, and this region and the ileum were not dilated. There was some enlargement of the mesenteric lymph nodes, especially marked in that portion of the mesentery containing the upper part of the jejunum. Microscopically, the mucosa of the duodenum appeared congested. There were some plasma cells and eosinophils in the tunica propria. Some desquamation of the epithelium was noted. There was no submucosal fat. The mucosa of the jejunum was congested and atrophied, with lymphocytic infiltration and connective tissue proliferation present, and it was covered by debris consisting of clumps of mucous cells and many plasma cells. There was congestion of the submucosa. The muscular layers were normal.

In several portions of the colon there was thinning of the wall, with pouching and with absence of normal haustrations. The appendix was normal.

Summary of Autopsy Observations—The pancreas was normal, the spleen was enlarged and the adrenal cortex was narrowed. The lower part of the esophagus was dilated, there was a healed ulcer at the cardiac portion. The small intestine showed remarkable changes. The third portion of the duodenum and the first 2 feet of the jejunum were dilated to twice the normal diameter, and there were extensive areas in this region which showed complete absence of the valvulae conniventes. Microscopic examination of the denuded areas showed mucosal atrophy, with lymphocytic infiltration and connective tissue proliferation. Between the denuded spaces many of the valvulae were hypertrophied and misshapen. The regional lymph nodes were markedly hypertrophied.

Synopsis of Case—A diagnosis of idiopathic steatorrhea was made in the case of a boy of 9 years who had been under observation by several physicians and in several hospitals since the age of 2½ years. Five years previously a clinical diagnosis of celiac disease had been made. An exploratory laparotomy had revealed "tetany" of the small intestine. The presenting symptoms were recurrent fatty diarrhea, fever, abdominal distention, recurrent gastrointestinal bleeding, hepatosplenomegaly and anemia. Roentgen examination showed typical "moulage" appearance of the duodenum and jejunum and marked dilatation alternating with spasm. There was progressive emaciation, and death from exhaustion. Autopsy showed a healed ulcer of the esophagus, an enlarged spleen, hypertrophied lymph nodes, a normal pancreas and narrowing of the adrenal cortex. The entire upper part of the small intestine was greatly dilated and was ballooned out in places. In the duodenum and jejunum complete atrophy of valvulae was demonstrated in the areas involved by the "moulage sign." This is believed to be the second recorded report of a case in which the roentgen appearance of the small intestine during life was confirmed by postmortem examination, and the first report in which the roentgen and postmortem protocols have been given in detail.

CASE 8—The patient, a single woman aged 47, was first seen Dec 7, 1938, at which time she complained of diarrhea and a burning sensation in the abdomen.

History—For years there had been attacks of abdominal distress, characterized by gas, a sensation of burning and, occasionally, nausea, which were attributed to "nerves." Twelve years previously a fibroid uterus and the appendix had been removed. For ten years there had been intermittent cramps in the legs, worse in winter. Four years previously she had fractured an arm by a fall. During the two weeks before admission there had been four to five frothy stools per day, and the tongue had been sore.

Physical Examination—The patient was 4 feet 10¾ inches (149 cm) in height and weighed 87 pounds (39.5 Kg). Since the ideal weight for that height is 124 pounds (56.2 Kg), her weight deficit was 37 pounds (16.8 Kg). The tongue was smooth at the edges but showed no ulcers. The abdomen was distended and tympanic. There was a bilateral carpal spasm on constriction of the upper arm (Trousseau sign) but no increased irritability of the facial nerve (Chvostek phenomenon).

Laboratory Data—The feces were collected for three days while the patient was on a standard Schmidt diet, which included milk and contained 142 Gm of fat per day. The total fat in the stools for the three day period was 1277 Gm, a loss of 30 per cent of the fat ingested as against a normal loss of about 5 per cent. The fatty acids constituted 72 per cent of the total fat, this indicated that the action of the pancreatic ferments was normal.

Except for increased indican in the urine, the other laboratory data were normal. The blood was studied by Dr. N. Rosenthal. The values for hemoglobin and red cells were high normal figures, presumably because of the increased hemoconcentration. The serum calcium was 9.2 mg and the phosphorus 3.1 mg per hundred cubic centimeters. The sugar tolerance test was as follows (values in milligrams per hundred cubic centimeters)

Fasting specimen	97.4
One-half hour after 50 mg dextrose (first dose)	136.0
One-half hour after 50 mg dextrose (second dose)	130.5

The test meal showed a free acidity of 27 and a total acidity of 54 (normal figures)

Roentgen Findings—On Dec. 8, 1938 the stomach was normal in size, shape, position, filling, tonus and peristalsis and was empty at five hours. The duodenal cap was complete. The remainder of the duodenum was greatly dilated and showed complete loss of valvulae ("moulage sign"). The jejunum was moderately dilated and showed coarseness or enlargement, rather than ironing-out, of the valvulae. The ileum seemed normal and was empty at nine hours. The filling of the colon was slightly accelerated, but its emptying was delayed, ninety-six hours and 4 stools were required to clear the barium. The opaque enema showed that it took 38 ounces (1,124 cc) of liquid (normal amount) to fill to the cecum. The splenic flexure was redundant and diaphragmatic in position but movable. The cecocolon was dilated, but the colon as a whole did not show the tremendous dilatation which is a characteristic in cases of marked carbohydrate intolerance. The gallbladder did not fill with dye after it was administered by mouth, despite the absence of diarrhea at the time, but reexamination after one month of treatment with bile salts showed distinct filling, only slightly fainter than normal.

When the barium sulfate meal was repeated, on Dec. 22, 1938, the duodenum and jejunum appeared more normal than at the first examination.

The patient's hand and forearm were compared with those of her sister, two years younger, and they showed a slightly diminished density of the radius and phalanges.

Summary of Roentgen Findings—In this patient the "moulage sign" was limited to the duodenum, the changes in the jejunum being minimal. Yet these findings seemed sufficient to suggest the diagnosis of idiopathic steatorrhea, which was confirmed by the examination of the stools. The only other important roentgen observation was the nonvisualization of the gallbladder, with subsequent visualization after treatment with bile salts.

Course—The diet was arranged in accordance with the feeding plan used for patients with sprue, except that, in view of the normal blood sugar curve, carbohydrates were fed with relative freedom. The diarrhea recurred during the three days of milk drinking imposed by the Schmidt test. Otherwise, the bowels moved once and twice a day and the stools were normally formed. Heartburn was soon controlled, but the flatulence responded slowly to treatment. The odor of the flatus was foul. The cramps in the legs were relieved by administration of calcium. On February 15 the diet included protein, 113 Gm, fat, 48 Gm, and carbohydrate, 422 Gm, the total number of calories was 2,487. The patient was taking six to eight bananas daily. The weight had reached 99 pounds (44.9 Kg) on May 3, 1939, a gross gain of 12 pounds (5.4 Kg) in almost five months. The appetite and strength were much improved. The treatment consisted of restricted diet and medication with bile salts.

Synopsis of Case History—The patient was a short woman of 47, whose weight was 30 per cent below normal. There was a positive Trousseau phenomenon. The roentgen study revealed that the "moulage sign" was limited to the duodenum and that the jejunum was involved slightly if at all. After the ingestion of dye the gallbladder did not visualize on the first examination, but reexamination after one month of treatment with bile salts showed a fairly dense concentration of dye.

COMMENT

Correlation of Roentgen and Postmortem Examinations—The present study shows that the changes seen roentgenographically in the small intestine in *advanced* idiopathic steatorrhea are based on loss or destruction of the valvulae conniventes and dilatation and thinning of the intestinal wall. This has been proved objectively by autopsy in a case in which roentgen examination during life showed the "moulage sign," together with segmentation and dilatation of the duodenum and jejunum. The results of autopsies recorded in the literature for similar cases have been extremely variable (Thaysen,¹⁰ Fairley¹¹). Loss of valvulae and thinning of the colonic wall have been found by some investigators but not by others. In only one previous instance, apparently, have roentgen studies been correlated with postmortem studies. This was a case, reported by Mendez Ferreira and Borgen,¹² in which the roentgen examination showed loss of valvulae and clumping of the barium in elongated masses, more marked in the ileum than in the jejunum. The results of postmortem examination were not given in detail, but there were atrophy of the mucosa and edema of the submucosa. The latter was particularly marked in the ileum, where, in addition, the Peyer patches showed atrophy.

That in advanced stages the intestinal tract may be damaged to a point where irreversible changes have occurred seems to be clear from the observations made in case 7. A similar opinion has been voiced by Snell.⁸

Just what anatomic changes accompany *less severe* forms of the disease is still undetermined. Mackie, Miller and Rhoads³ studied sections of the small intestine in cases of ulcerative colitis associated with deficiency disease. They stated the belief that in their cases intestinal abnormalities similar to those of sprue had been shown by roentgen examination, and in their histologic preparations they noted edema of the mucosa and submucosa and slight infiltration of mononuclear wan-

10 Thaysen, T. E. H. *Non-Tropical Sprue*, Copenhagen, Levin & Munksgaard, 1932.

11 Fairley, N. H. *Sprue: Its Applied Pathology, Biochemistry and Treatment*, Tr. Roy. Soc. Trop. Med. & Hyg. **24**: 131-179, 1930.

12 Mendez Ferreira, A. E., and Borgen, J. A. *So-Called Nontropical Sprue Associated with Tuberculosis of the Lymph Nodes*, Proc. Staff Meet., Mayo Clin. **12**: 289-294, 1937.

dering cells and lymphocytes. In this connection the reversibility of the mucosal alterations is again of practical interest. In less advanced disease, such as was present in cases 4, 5 and 8 of the present series, it has been shown that with proper treatment the "moulage sign" may disappear, or at least regress. This phenomenon, which suggests that the valvulae conniventes are restored to normal, has also been observed by Snell and Camp² and by Mackie, Miller and Rhoads.

The next question that arises is what happens in cases in which the degree of severity of the disease is intermediate. These are characterized by the presence of dilatation, as shown by roentgen examination, in spite of which recovery takes place. Case 6 is such an instance. Here the dilatation was marked, but, unlike the patient in case 7, who died, the patient improved steadily, and there is at present some evidence that the bowel is slightly less abnormal than it was at first. Only time can tell how far the improvement, as seen roentgenographically, will go.

To summarize the factors in regard to prognosis, it may be stated that in the mild form of the disease, in which the "moulage sign" is the only positive roentgen sign, the progress of the disease is reversible, but that in advanced disease, in which dilatation and atrophy of the wall of the bowel have supervened, a restitutio ad integrum, though perhaps still possible, is not very likely.

That the duodenum may be the only site of the "moulage sign" is demonstrated by the observations in case 8 of the present series. Up to that time the jejunum had been the chief site of involvement noted in my cases.

Practical Value of "Moulage Sign" Confirmed—My experience so far has confirmed the clinical impression that in so-called idiopathic steatorrhea the significant, if not the only, abnormality, is disturbance in absorption by the small intestine. In the only case in this series in which autopsy was done the pancreas was anatomically normal. This supports the view that idiopathic steatorrhea, which includes celiac disease, is to be sharply distinguished from the congenital steatorrhea, due to cystic fibrosis of the pancreas, recently described by Andersen¹³ in this country and by Harper¹⁴ in Australia. I believe that the roentgen signs are of practical value, even though my original statement may have to be modified by further experience, particularly in view of the fact that cases of known pancreatic disease have not yet been available to me for comparative study.¹⁵

13 Andersen, D. H. Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease. A Clinical and Pathologic Study, *Am J Dis Child* **56**:344-399 (Aug.) 1938.

14 Harper, M. H. Congenital Steatorrhea Due to Pancreatic Defect, *Arch Dis Childhood* **13**:45-56, 1938.

15 Snell has just reported that he observed similar roentgen phenomena in 3 cases of pancreatogenous diarrhea, but this disease seems to be much less common than idiopathic steatorrhea.

Role of Biliary Tract in Idiopathic Steatorrhea—The failure of the gallbladder to fill with dye in idiopathic steatorrhea has been further confirmed. Case 8 is the fourth consecutive case in which the gallbladder either failed to visualize or did so very faintly. Unfortunately, in no case was it practical to make a control examination after the intravenous injection of the dye. This procedure would help to prove whether the nonfilling is due to failure of the intestines to absorb the dye or to some associated disease of the biliary tract. The latter possibility has been suggested by Pillai and Murthi¹⁶ and, more recently, by Hopman.¹⁷ Radl and Fallon¹⁸ also report a case of nontropical sprue in which the gallbladder was not visualized. Improvement in function of the gallbladder, as determined roentgenologically, followed the oral administration of bile salts in the 2 cases in which follow-up studies were available. The observation in case 4 that pain was best relieved by acetylsalicylic acid, a known cholagogue, may also be considered as suggestive evidence that an abnormal biliary status may be associated in some way with idiopathic steatorrhea. Clinically, the use of bile salts seems justifiable in the treatment of idiopathic steatorrhea.

Role of Adrenal Cortex in Idiopathic Steatorrhea—The thinning of the adrenal cortex in case 7, in the presence of lymphatic hypertrophy and splenomegaly, seems to support the theory that insufficiency of the adrenal cortex may play a role in the etiology of idiopathic steatorrhea. In his recent monograph, Verzar¹⁹ has advanced the theory that the capacity of the intestine to absorb fats and carbohydrates is closely associated with the activity of the adrenal cortex. Decreased activity of the adrenal cortex is apparently responsible for lack of absorption, and, experimentally, replacement therapy aids absorption. Dr. David Perla, of the department of pathology of Montefiore Hospital, was asked to discuss the significance of the autopsy observations in case 7 from this point of view, he replied as follows:

The thinning of the cortex of the adrenal, in spite of the deposition of lipid, may mean a decreased activity of the cortex. The presence of lipid does not necessarily reflect the state of activity of the gland. It is not possible to state definitely from the histologic observation whether the adrenal cortex is in an exhausted state, since in all cachectic states lipoids are apt to increase in the adrenal cortex. Such increases do not, however, indicate an increase in cortical hormone but rather point to some type of storage of cholesterol.

16 Pillai, M. J. S., and Murthi, K. N. Further Observations on the Radiological and General Findings in Sprue, *Calcutta M. J.* **30** 225-230, 1935.

17 Hopman, B. C. Etiology of Tropical Sprue and Related Disease, *Geneesk tijdschr. v. Nederl.-Indie* **78** 904, 1938, abstracted, *J. A. M. A.* **111** 214 (July 9) 1938.

18 Radl, R. B., and Fallon, M. Nontropical Sprue with Duodenal Involvement and Tetany, *Arch. Int. Med.* **50** 595-604 (Oct.) 1932.

19 Verzar, F. Absorption from the Intestine, New York, Longmans, Green & Co., 1936.

However, the presence of marked lymphoid hyperplasia and of splenomegaly with enlargement of the lymphoid follicles of the spleen is strongly suggestive of diminished activity of the adrenal cortex. Experimentally, removal of the adrenal glands is followed by pronounced hyperplasia of the lymphoid tissue and a regeneration of the thymus as well as by enlargement of the spleen. In the presence of an exhausting disease, especially of idiopathic steatorrhea, in which there is an additional factor of dehydration due to diarrhea, one would expect marked exhaustion of lymphoid tissue and atrophy of the thymus and of the spleen. The presence of the reverse, therefore, is strongly suggestive of a factor of adrenal cortical insufficiency in the pathogenesis of idiopathic steatorrhea.

In short, the observations at autopsy in this case lend some support to the theory that insufficiency of the adrenal cortex may in some way be associated with idiopathic steatorrhea resulting from failure of intestinal absorption.

Occurrence of Pain and Hemorrhage in Idiopathic Steatorrhea—Pain and hemorrhage are not usually described in idiopathic steatorrhea, but in 2 of the cases so far observed they were prominent complications. The pain has been ascribed to intestinal spasm, although atypical left-sided biliary (gallbladder) colic may also possibly play a role in this connection. The nature of the bleeding is not clear. Holst⁷ reports a case of this sort and so does Snell⁸. Coincidental "peptic" ulceration cannot be excluded (case 7). Another possible cause is some failure of coagulation of the blood (case 4) possibly due to lack of absorption of calcium or essential vitamins (vitamin K) or to insufficiency in biliary secretion. In fact, Snell has just reported that in 1 of his cases the prothrombin content of the plasma was reduced by more than 50 per cent.

SUMMARY

The 6 cases originally reported as instances of idiopathic steatorrhea have been summarized and brought down to date.

Reports of 2 new cases are presented. One of these is believed to be the first in which a detailed description is given of postmortem examination which confirmed the characteristic roentgen findings in idiopathic steatorrhea. In this case roentgen examination showed a marked "moulage sign" plus dilatation and segmentation of both the duodenum and the jejunum, postmortem examination showed that these were the sites of complete loss of the valvulae conniventes. The second case suggested that the "moulage sign" may be limited to the duodenum, with little if any involvement of the jejunum.

Evidence is gradually accumulating concerning the reversibility of the intestinal changes in idiopathic steatorrhea. In the mild form of the disease, in which only the "moulage sign" is present, the changes seem to be reversible. In far advanced stages with superadded segmentation and dilatation, a complete restitutio ad integrum seems unlikely.

Further experience with the roentgen study of the small intestine shows that this method is of value in the demonstration of steatorrhea. Whether the characteristic intestinal changes are specific for idiopathic steatorrhea, as was originally believed, or whether they are also present in other forms of steatorrhea remains to be determined.

There is increasing evidence that the biliary tract may play an etiologic role in idiopathic steatorrhea. Failure of the gallbladder to fill with dye in the normal way continued to occur in those cases in which the gallbladder was studied roentgenologically²⁰. Whether this phenomenon is due to impaired intestinal absorption or to some other cause is still undetermined. The administration of bile salts seems to improve the function of the gallbladder. Since bile salts are believed to aid in the absorption of fat, their use is tentatively recommended in the clinical management of idiopathic steatorrhea.

Bleeding and pain may occur in cases of idiopathic steatorrhea.

²⁰ More recent experience has shown that the gallbladder may visualize quite normally in some cases of idiopathic steatorrhea.

GENERALIZED SARCOIDOSIS OF BOECK

A CLINICAL REVIEW OF ELEVEN CASES, WITH STUDIES OF THE
BLOOD AND THE ETIOLOGIC FACTORS

GEORGE T HARRELL, M D

DURHAM, N C

The opportunity of following 11 instances of generalized Boeck's sarcoid over a period of several years has presented unusual chances to study the progress of the disease from the clinical, metabolic and etiologic viewpoints. The clinical aspects of the disease have been discussed by numerous authors,¹ and Hunter² has presented a full historical review. A great variety of syndromes which resemble sarcoid probably can be grouped together.³

Little has been written on the metabolic changes associated with the disease. The relation of calcium metabolism to the cystlike osseous lesions and of protein metabolism to the activity of the disease and to lesions in the liver have been discussed.⁴

Etiologic studies in the past have been directed chiefly toward the demonstration of tubercle bacilli in the lesions. The use of various animals, usually guinea pigs and to a less extent rabbits and pigeons, has given disappointing results. Smaller animals, such as mice and rats, rarely have been used, in spite of the fact that rats react with a sarcoid-like lesion to tubercle bacilli and do not become allergic to tuberculin.⁵ Cultural studies have resulted in the inconstant observation of a

From the Department of Medicine, Duke University School of Medicine and Duke Hospital

1 (a) Longcope, W T, and Pierson, J W. Boeck's Sarcoid (Sarcoidosis), Bull Johns Hopkins Hosp **60** 223, 1937. (b) Schaumann, J. Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, Brit J Dermat **48** 399, 1936.

2 Hunter, F T. Hutchinson-Boeck's Disease (Generalized "Sarcoidosis") Historical Note and Report of a Case with Apparent Cure, New England J Med **214** 346, 1936.

3 Pinner, M. Non-Caseating Tuberculosis. An Analysis of the Literature, Am Rev Tuberc **37** 690, 1938.

4 Harrell, G T, and Fisher, S. Blood Chemical Changes in Boeck's Sarcoid with Particular Reference to Protein, Calcium and Phosphatase Values, J Clin Investigation **18** 687, 1939.

5 Jadassohn, W. L'origine tuberculeuse de la maladie de Boeck, Bull Soc franç de dermat et syph **41** 1344, 1934.

variety of organisms^{1b} Longcope and Pierson^{1a} have attempted to grow fungi from the lesions on Sabouraud's medium but have had no success. Serologic studies with the organisms recovered from lesions and with stock strains of tubercle bacilli have been made by Schau-mann^{1b}. Little attempt to apply similar methods to fungi has been made.

TABLE 1—*Distribution*

	Case 1 Age, 26 Negro Male			Case 2 Age, 23 Negro Female	Case 3 Age, 27 Negro Female			Case 4 Age, 22 Indian Male	
Date	8/1/34	12/11/34	10/14/38	6/9/36	12/3/36	10/28/37	9/15/38	3/16/37	9/26/38
Duration	4 mo	8 mo	4 yr	12 mo	7 yr	8 yr	9 yr	12 mo	2½ yr
Activity	A	A	I	A	A	A	A	A	A
Weight loss	27 lbs	30 lbs	15 lbs	15 lbs	30 lbs	23 lbs		20 lbs	23 lbs
Temperature peak (Centigrade)	37.2	38.3		37	38.3			37.6	38.4
Skin									
Nares									
Lids	+	+		+					
Head		+		+		+	Scars		
Trunk				++	+	+	Scars		
Extremities			Scars	++	+		Scars		
Perineum				++			Scars		
Mucous membranes	+								
Lymph nodes									
Auricular			+		++	++	+	+	++
Mandibular	+				++	++	++	+	++
Cervical	++	++			++	++	++	++	++
Epitrochlear		+			+			+	
Axillary		++			+	+++	++++	++	+
Inguinal	+	+++			+++	++++	++++	++	++
Mediastinal	++	++			+++	+++	+++	++	+++
Others					++	++	++	+	++
Other locations									
Lung	+++	++++	Clear	+++	±	±	±	0	0
Rales	+		0	0	0		0	+	0
Bone		0	0	±	++	++	+++	0	0
Eye	0	0	Scars	0	0	±	0	++	Scars
Tonsils	+		+	+					
Liver	+	0		0	0	+	0	0	0
Spleen	0		0	0	0		+	0	0
Miscellaneous	Muscle, orbit	Parotid, pharynx	Epididymus			Lacrimal	Parathyroid?		
Biopsy									
Skin				+	+				
Node							+	+	
Other	Muscle	Parotid							
Treatment	Rest, cod liver oil			Rest, cod liver oil, neoarsphenamine for syphilis	Ultra violet radiation	Intra venous typhoid vaccine		Cod liver oil, ultra violet radiation, neoarsphenamine	
Result	Worse	Gaining weight	Well for 2 years	Slight improvement in 27 mo		Improved, best for 2 years	Nodes growing		Nodes growing, eyes well

previously in etiologic studies. The use of cutaneous tests has been confined to reactions to tuberculin and the interesting unconfirmed reaction to excised tissue of human beings, reported by Williams and Nickerson,⁶ and this work has been repeated on the patients reported here, extracts of lymph nodes being used instead of skin. Allergic

6 Williams, R. H., and Nickerson, D. A. Skin Reactions in Sarcoid, *Proc Soc Exper Biol & Med* 33:403, 1935.

studies have been done only in regard to the proteins of the tubercle bacilli

The pathologic changes in surgical material have been described many times, and instances of sarcoid observed at autopsy have been reported with complete studies by Schaumann^{1b} and Nickerson⁷ Excellent

of the Lesions

Case 5 Age, 27 Negro Male		Case 6 Age, 21 Negro Male	Case 7 Age, 27 Negro Female			Case 8 Age, 36 White Male	Case 9 Age, 32 Negro Female		Case 10 Age, 30 Negro Male	Case 11 Age, 30 Negro Male
5/3/37	4/27/39	6/16/37	6/14/38	10/18/38	5/18/39	8/16/38	11/7/38	5/26/39	2/24/39	4/4/39
2 mo A 20 lbs 37 6	2 yr I 0 37	18 mo A 36 9	10 wk A 25 lbs 39 2	7 mo A 16 lbs 37 4	1 yr A 0 37 5	4 mo A 40 lbs 37 5	6 yr A 0 37 4	6½ yr A 0 37 6	9 yr A 25 lbs 38	5 yr A 0 38 2
		+					+++	+++		+++
	+	+				+	++	+++		+
	+						++	++		+++
		+					++	++		+
							+++++	+++++		++
							++	++		+
+		+			+	+				
+++	+	+	+	++	+	+			+	+
++		+	++	+	+	++			+	++
+++++		+	+	+	+	+		+	+	++
++		+	+	+	+	+			++	+
+++++	+	+	++	++	++	+			++	+
++		+	++	+++	++		±		±	
+		+	++	++		+				++
0	0	0	0	0	0	+++	++	++	+++	+++
0	0	0	0	0	0	0	0	0	+	±
0	0	0	0	0	0	±	0	0	±	-
0			±	0	+	+	0	±	0	0
			0		+	+	0	±	0	0
										Pharynx
		++					+			±
++		+	+	+		+			++	+
15 intra venous injections neoarsphen- amine, 0.45 Gm	Well in 21 mo	Cod liver oil	Rest, cod liver oil	Cod liver oil		Rest, cod liver oil	Ultraviolet radiation		Rest, cod liver oil, antisyphilitic treatment	1,360 roent gen units
			Gaining weight	Nodes unchanged		No improve ment				

lent reproductions of roentgenograms of the chest and of bones⁸ are available. The hematologic picture and an increase in the sedimentation

7 Nickerson, D. A. Boeck's Sarcoid. Report of Six Cases in Which Autopsies Were Made, Arch Path 24:19 (July) 1937

8 Snapper, I., and Pompen, A. W. M. Pseudo-Tuberculosis in Man, Haarlem, de Erven F. Bohn, 1938

rate have been recorded in some instances. Electrocardiographic changes have been described⁹ but are not specific.

These varied data are recorded for different groups of patients. All the changes rarely have been followed in a single group of patients suffering from Boeck's sarcoid. The present etiologic studies were undertaken to obtain additional data by using (1) species of animals not used by others in the attempt to isolate acid-fast organisms, (2) cutaneous tests, cultures and serologic tests for fungi and other organisms, and (3) the cutaneous test of Williams and Nickerson. Metabolic studies



Fig 1 (case 9) —Patient with nodules on the eyelids and destruction of the nares

were directed toward (1) the relation of the cystlike osseous lesions to calcium, phosphorus and phosphatase activity and the occurrence of abnormal proteins in the urine, (2) the location of the lesion responsible for the hyperglobulinemia, and (3) the variations in the concentration of constituents of the blood with changes in the activity of the lesions.

CLINICAL DATA

The present series of patients with the generalized form of Boeck's sarcoid, composed of 11 patients observed since 1934, is the largest yet

⁹ Salvesen, H. A. The Sarcoid of Boeck. A Disease of Importance to Internal Medicine, *Acta med Scandinav* 86:127, 1935.

reported in the United States and is the first from the South. The series reported by Longcope and Peison^{1a} is the only other group in which Negroes predominated, the disease has not been previously reported as occurring in the American Indian. The occurrence primarily in young adults is in accord with the experience of others. Two cases, in which the disease was of five and twenty-seven months' duration, respectively,

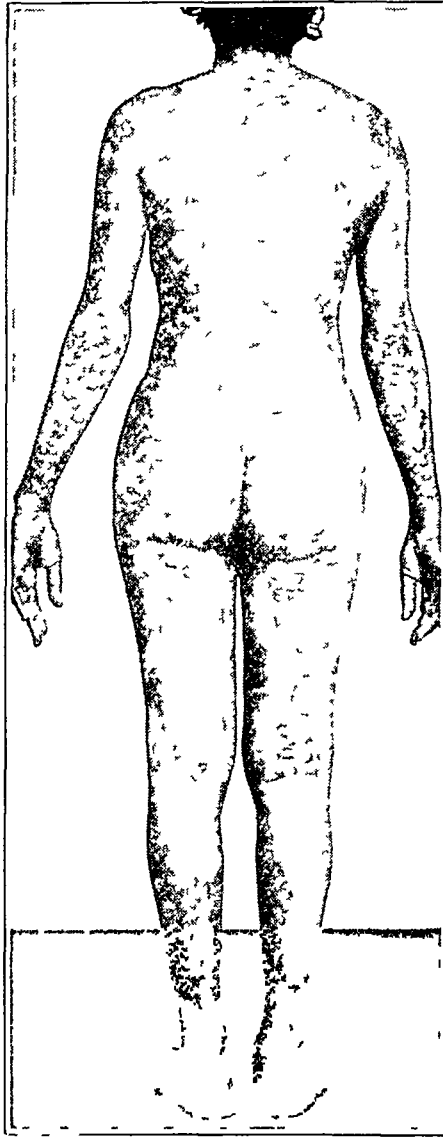


Fig 2 (case 9) —Generalized distribution of cutaneous lesions

have been restudied twenty-one and twenty-nine months after clinical recovery. The condition in the majority of the cases in the literature is of relatively long duration, it is possible that cases in which the condition is of short duration have been overlooked or wrongly diagnosed in the past.

The distribution of the lesions in the body is given in table 1. Lesions of the skin were the predominant ones in 4 cases and generally were in

the form of painless papules 1 to 5 mm in size, with no surrounding erythema, induration or anesthesia, they occurred most frequently on the face, arms and legs. The skin was dry, and the lesions tended to have small scales or crusts but did not itch or become purulent. The occurrence along the margin of the eyelids should be especially emphasized, for this phenomenon is infrequent in other diseases involving the skin (fig 1). Destruction and distortion of the nares was prominent in 2 instances (fig 1). In 2 cases almost the entire body was involved, but the palms and soles were spared, the lesions were of varied shapes, ranging from annular to circinate (fig 2). Lesions were occasionally



Fig 3 (case 4) —Patient with enlargement of postauricular, posterior cervical and occipital lymph nodes

noted in the scalp, on the mucous membranes and around the rectum or perineum.

Enlargement of the peripheral lymph nodes was the most prominent feature in 5 cases and occurred in all but 2 of the other cases. The nodes ranging up to 4 by 6 cm in size were firm, rubbery, discrete, movable and painless, though painful nodes were present in case 5. Usually all the nodes were enlarged, though some groups were more prominent than others, enlargement of the epitrochlear, submental, preauricular and postauricular nodes should be emphasized (fig 3). Enlargement of nodes along the borders of the muscles of the shoulder girdle or along the course of the major lymphatic vessels of the arm is rarely observed.

in other conditions. Schaumann has emphasized that even the small nodes will show lesions when excised, and I have observed this generally to be true.

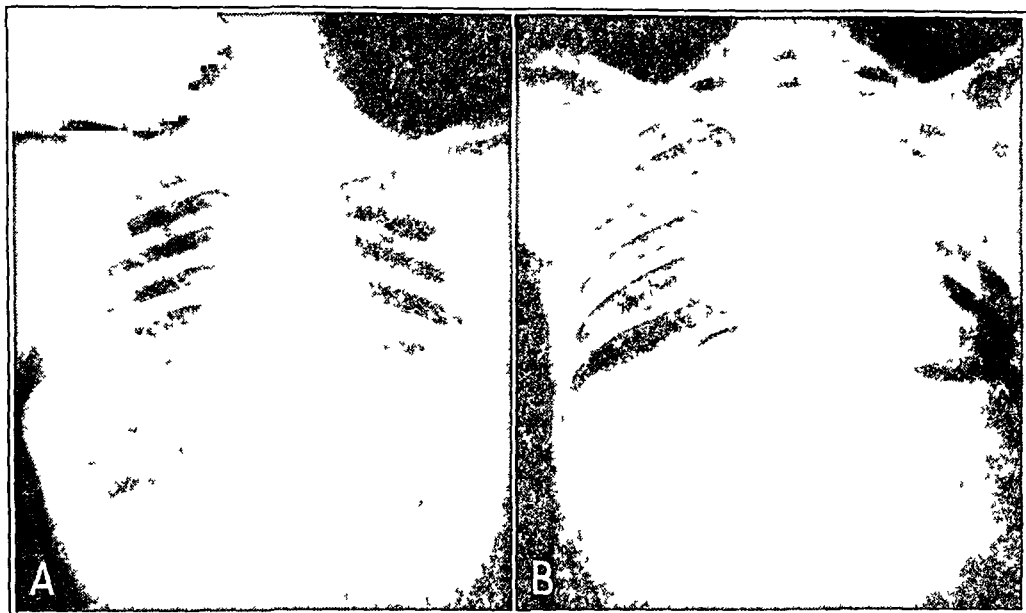


Fig 4—*A* (case 3), peribronchial fibrosis and enlarged mediastinal lymph nodes, *B* (case 10), diffuse infiltration in the central part of the lungs, sparing the apices

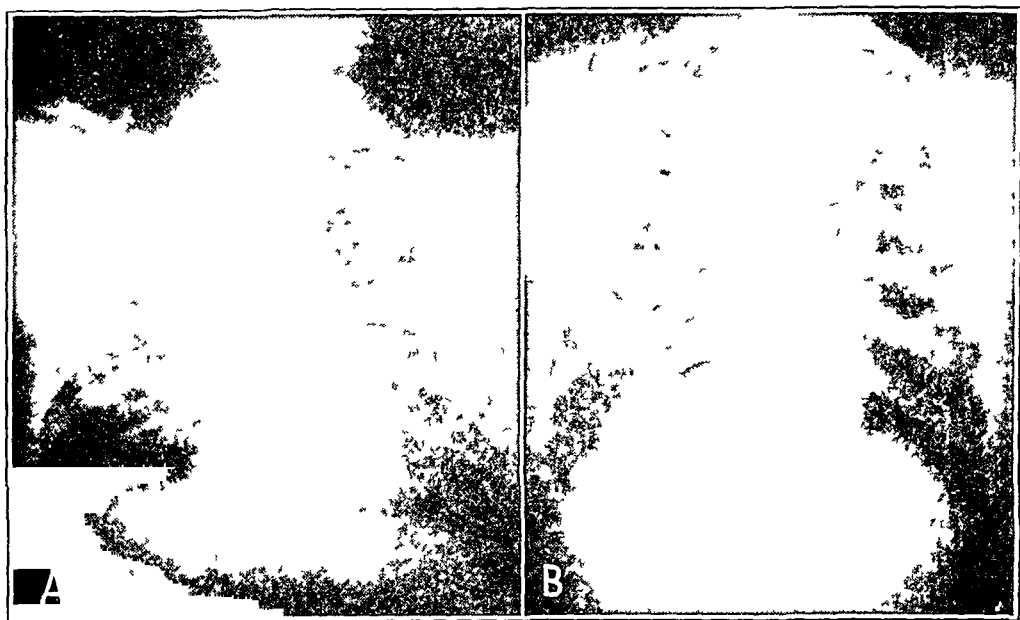


Fig 5—*A* (case 1), miliary infiltration, acute phase, *B* (case 11), generalized diffuse fibrosis, most marked in the central portion of the lung

Distinction should probably be made between enlargement of the peripheral and that of the mediastinal nodes, for the latter often accompany lesions of the lungs and may occur with only moderate peripheral enlargement (fig 4 *A*). Lesions in the lung fields were of three types (1) peribronchial fibrosis and thickening, usually extending downward

symmetrically into the lower lobes (fig 4 *A*), (2) soft infiltration in the midlung fields sparing the apexes (fig 4 *B*), and (3) areas resembling miliary tuberculosis, with a fine marbled or reticulated appearance (fig 5 *A*). In case 1 extensive miliary areas radiating from the hili completely disappeared, and four years later only slight peribronchial thickening remained (fig 6). No essential change in the lungs has occurred in 3 other patients who have had serial roentgenograms taken over periods greater than one year. Rales were heard in 4 instances, while friction rubs were audible once. Pain in the chest, usually without physical signs, was a frequent symptom and occurred as a rule in the axilla or under the scapula.

Roentgen ray studies of the bones were made, as shown in table 2. Trabeculation and cyst formation in the hands and feet (fig 7) and

TABLE 2—Roentgen Ray Studies

Date	Case 1			Case 2	Case 3			
	8/1/34	12/11/34	10/14/38		12/3/36	7/6/37	10/13/37	9/15/38
Bones								
Hands			0	±	+++	+++	+++	+++
Feet					++		++	+++
Long bones		0					+	
Skull					±	0		0
Spine					0		0	
Pelvis					0		0	
Ribs	0	0	0	0	0	0	0	0
Chest								
Swollen nodes	++		0		++	+++	+++	+++
Peribronchial thickening			±		+	+	+	+
Infiltration of the middle portion of the lungs				+++				
Miliary areas	+++	++++	0					

cysts of the tibia, ulna and cuneiform bone were seen. The cystlike lesions appeared to be sharply punched out, with little change in the density of the surrounding bone; pathologically these areas are composed of sarcoid tissue in bone. Progression was noted over a period of two years in the cysts of the toes in case 3. Except for areas suggesting rarefaction in the ribs and decalcification in the hands, each noted once, no change was found in the bones of any of the other patients. Schauermann has pointed out that the degree of bone marrow involvement cannot be judged by the roentgen ray observations, for foci of involvement can be found by pathologic examination of the tissue when none appear in the films.

Longitudinal ridging of the nails occurred in 1 case (fig 8). The lesion apparently is associated with changes in the bones and hence probably with actual invasion of the nail bed as well as interference with its blood supply. The nails are often brittle, even though no ridging is apparent. The tips of the fingers are often misshapen, and the skin

over the base of the nail, atrophic and shiny The same changes may occur in the toes

Invasion of the eye, producing iridocyclitis and keratitis, occurred in case 4 Under the slit lamp the yellowish white irregularly shaped opacities in the cornea resolved into numerous discrete "mutton fat" amorphous deposits on Descemet's membrane They cleared up over a period of eighteen months, though the lesions elsewhere in the body showed no regression Patient 1 showed no nodules in the eye when he was first seen, but scars were present four years later In case 10 there had been an iridectomy six years previously, supposedly because of a syphilitic iritis which did not respond to antisiphilitic therapy, the condition may have been sarcoid at that time The invasion of the lids noted in 5 cases has been mentioned, the periorbital tissues at the canthus of

of the Bones and the Chest

Case 4		Case 5		Case 6	Case 7			Case 8	Case 9		Case 10	Case 11
3/16/37	9/29/38	5/3/37	4/27/39	7/16/37	6/14/38	10/17/38	5/19/39	8/16/38	11/7/38	5/26/39	2/27/39	4/4/39
0	0	0	0	0		0		±	0	0	0	±
0			0				±	0			0	±
					0							
0	0	0	0	0	0	0	0	0	0	0	±	0
++	++++	++	+	++	++	+++	++		±	±	±	
			+	++		+	+					
	++			+				+++			+++	+++
									++	++		

the eye were invaded once and the lacrimal gland was enlarged in 1 instance

The skeletal muscles were extensively invaded in case 1 (fig 9) A transient paralysis of the left internal rectus muscle was noted, probably due to invasion of this muscle, though invasion of nerve tissue cannot be excluded Nodules were noted along the epididymis in 1 instance

Occasional enlargement of the liver and spleen without jaundice or ascites was noted Although Schaumann stated that abnormalities of the tonsils occurred in a large percentage of the cases, I noted only occasional enlargement Involvement of the nasal septum was not found In addition to patient 1, in whom the parotid gland was invaded, a 27 year old Negress, not studied in sufficient detail to be included in this series but with the diagnosis proved by biopsy, presented the typical picture of uveoparotid fever ^{9a}

^{9a} This case was subsequently reported as case 6 of Thompson, W C Uveoparotitis, Arch Int Med 59 646 (April) 1937



Fig 6 (case 1) —Rontegenogram showing residual peribronchial fibrosis, taken four years after figure 5*A*



Fig 7 (case 3) —Trabeculation and formation of cystlike lesions in the fingers

Accentuation of the pulmonic second sound was noted in 2 cases in which the condition was of long duration, and there was splitting of the sound in others. This observation was interpreted as evidence of developing pulmonary hypertension because of the fibrosis in the lungs. Early clubbing of the distal phalanges was noted in only 1 instance.

Among the symptoms noted were weakness and fatigability, anorexia, loss in weight, pains in the joints, muscular stiffness, cough and pain in

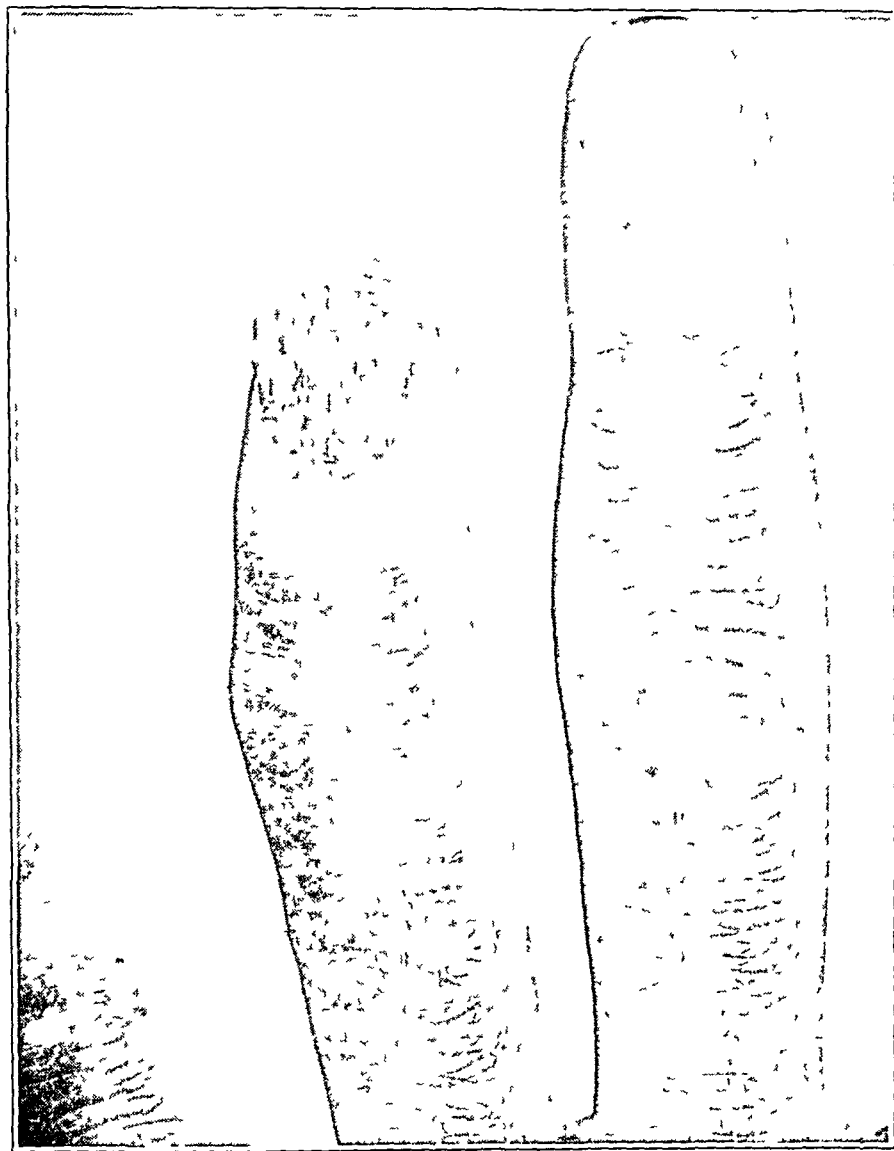


Fig 8 (case 3) —Longitudinal ridging of the nail and bulbous swelling of the middle phalanx

the chest. Loss in weight, ranging up to 40 pounds (18 Kg) in five months, occurred in all but 1 patient. Cough and transient pains in the chest often were present in the absence of demonstrable lesions in the lungs. Pains in the joints were usually not accompanied by demonstrable lesions. Fever was conspicuously absent, only rare observations above 38 C were made. Few patients had noted fever at home.

PATHOLOGIC OBSERVATIONS

The most striking pathologic observation was the complete absence of inflammation in the tissues surrounding the lesions. In only 1 instance was the capsule of the lymph node found thickened or adherent to adjacent structures. The biopsy incisions healed promptly in all cases but 1, and in that case healing followed the removal of a buried suture.



Fig 9 (case 1) —Section of acute lesion of the muscle showing giant cell with vacuoles, moderate lymphocytic infiltration of the tubercle and no surrounding or perivascular inflammation ($\times 110$)

No necrosis was noted in the gross specimens. The lesions often were yellow before fixation.

Microscopically, the lesions were composed of groups of epithelioid cells, usually arranged in round forms resembling tubercles. In lymph nodes this reaction usually completely replaced the lymphoid tissue without involvement or thickening of the capsule. Small areas of necrosis

were occasionally observed in the centers of the tubercle-like lesions. Little fibrosis was found between the collections of tubercles, but in the lesions of long duration the connective tissue present was often hyalinized (fig 10). Congo red stains for amyloid on such tissue occasionally gave positive results. Rare giant cells, usually of foreign body type and containing up to twenty nuclei, were seen, they occurred more fre-



Fig 10 (case 3) —Section of a chronic lesion of the axillary lymph node showing epithelioid cells and hyalinization of connective tissue, with amyloid-like tissue at far right ($\times 110$)

quently in the presence of necrosis. Small lymphocytes were usually found scattered among the epithelioid cells. No eosinophils or polymorphonuclear leukocytes were observed, and no endarteritis or perivascular infiltration was noted. In rare giant cells clear vacuoles were seen (fig 9), and in lesions of long duration fat cells were found around the periphery of the lymph nodes, stains for fat were not used, however

No fungi were noted with hematoxylin and eosin or bacterial stains. Stains for acid-fast organisms were used on all sections and the results controlled in many cases by checking with slides known to show the bacilli. MacCallum or Brown bacterial stains were used on many sections. No organisms were found with any stain.

Instances which were not recorded as cases of sarcoid in the clinical record library were rediscovered during a review of several hundred microscopic sections from patients whose disease was diagnosed as tuberculosis. The cases of sarcoid often were placed in this classification, even when the diagnosis was suspected clinically and confirmed by biopsy.

TABLE 3—*Microscopic*

	Case 1			Case 2	Case 3			Case 4	Case 5	
Date	8/31/34	12/22/34		6/10/36	12/8/36		9/16/38	3/10/37	5/10/37	5/15/37
Site	Muscle of the arm	Parotid gland	Epitrochlear node	Skin of the arm	Skin of the arm	Epitrochlear node	Axillary node	Deltoid node	Epitrochlear node	Cervical node
Gross examination										
Thick capsule		0	0			0	0			
Microscopic examination										
Necrosis	0	0	0	0	0	0	0	0	0	0
Fibrosis	++	+++	+++	+	++	++	++	+	+	+
Tubercles	++	+++	+++	+++	+	++	++	+++	++	++
Necrosis	Rare	+	+	0	Rare	0	0	0	Rare	Rare
Giant cells	Rare	+	+	Rare	0	0	Rare	Rare	Rare	Rare
Epithelioid	+++++	+++++	+++++	+++++	+++++	+++++	+++++	+++++	+++++	+++++
Lymphocytes	++	+++	+++	+	+	++	+	++	++	++
Eosinophils	0	0	0	0	0	0	0	0	0	0
Polymorphonuclears	0	0	0	0	0	0	0	0	0	0
Fungi	0	0	0	0	0	0	0	0	0	0
Bacteria					0	0		0	0	0
Acid fast	0	0	0	0	0	0	0	0	0	0
Original diagnosis										
Clinical	Tuberculosis	Fungus		Sarcoid	Sarcoid		Sarcoid	Sarcoid	Sarcoid	Sarcoid
Pathologic	Tuberculosis	Tubercle reaction		Sarcoid	Sarcoid		Sarcoid	Sarcoid	Sarcoid	Sarcoid

LABORATORY DATA

The laboratory data are presented in table 4. Four patients had a mild hypochromic anemia. The white blood cell count was usually normal or only slightly elevated. I was unable to confirm the impression of some observers that the stab forms are increased, although an increase was noted during intravenous therapy with typhoid vaccine in case 3. In all cases there were eosinophils at some time, and basophils in small numbers were usually present. By making repeated differential counts and by grouping the large lymphocytes and monocytes together, I could confirm the "showers" of large mononuclear cells noted by others. The rise usually appeared to be at the expense of the polymorphonuclear leukocytes. The "showers" could not be correlated with changes in temperature or clinical developments. Abnormal cells were rarely seen.

Of the cases in which the sedimentation rate of the red blood cells was determined, it was increased in those in which the condition was active, and in the 2 cases in which the condition had healed it returned to normal

The changes in blood chemistry have been discussed in detail in another paper⁴ The serum proteins were above 8 Gm per hundred cubic centimeters in 8 instances, but the albumin-globulin ratio was reversed in all cases in which the condition was active In 2 cases in which the condition had healed the total proteins and the albumin-globulin ratio were normal, in 1 instance, however, determinations had not been made during the active stage Changes in the serum globulin

Examination of the Lesions

Case 6			Case 7		Case 8	Case 9	Case 10		Case 11	
6/25/37			6/20/38	10/18/38	8/19/38	11/9/38	4/24/39	4/25/39	4/5/39	
Skin of the neck	Lip	Cervical node	Cervical node	Inguinal node	Supraclavicular node	Skin of the abdomen	Inguinal node	Axillary node	Skin of the face	Inguinal node
			+	0	0					
0	0	0	0	±	0	0	0	0	0	0
++	++	+	+	+	++	+	+	+	+	+++
++++	++++	++	++	+++	++	+++	+	0	+++	++
0	0	0	Rare	±	+	0	0	0	+	0
0	Rare	Rare	Rare	++	Rare	+	0	0	+	Rare
+++++	+++++	+++++	+++++	+++++	+++++	+++++	++	+	+++++	+++++
++	++++	+	++	++	++	+	0	0	+	+
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
Sarcoid			Hodgkin's disease	Sarcoid	Lympho sarcoma	Sarcoid	Tuber culosis	Sarcoid	Sarcoid	Sarcoid
Tuber culosis			Tuber culosis	Sarcoid	Sarcoid	Sarcoid	Sarcoid	Reticulo endothelial hyperplasia	Sarcoid	Sarcoid

may be of prognostic import The blood calcium level was increased beyond normal limits in 6 cases and was at the upper limit of normal in 2 others The calcium tolerance test of London and Bernheim¹⁰ gave peaked, flat and plateau curves The blood phosphorus was not increased, but the phosphatase was increased at some time in 7 cases in which it was determined and in which the condition was active The observations could not be correlated with the site or extent of the lesions or with the duration of the disease A low or normal cholesterol level was observed in 7 cases in which the condition was active A higher value was obtained in a case in which the condition was active and of short duration and subsequently healed and in a case in which the con-

¹⁰ London, I M, and Bernheim, A R Calcium Tolerance Curves in Paget's Disease of the Bone, J Lab & Clin Med 23 18, 1937

TABLE 4—Results of Laboratory Tests

Case	Date of Admission	Total Protein, Gm per 100 Cc	Albumin, Gm per 100 Cc	Globulin, Gm per 100 Cc	Calcium, Mg per 100 Cc	Phosphorus, Mg per 100 Cc	Phosphatase, Bodansky Units	Cholesterol, Mg per 100 Cc	Bilirubin Tolerance Retention, per Cent	Sedimentation Rate, Mm per Hour	Hemoglobin, Gm per 100 Cc	Red Blood Cells, Millions per Cu Mm	White Blood Cells per Cu Mm	Polymorphonuclears, per Cent	Stab Cells and Juvenile Forms, per Cent	Eosinophils, per Cent	Basophils, per Cent	Small Lymphocytes per Cent	Large Lymphocytes per Cent	Monocytes, per Cent	Bence Jones Protein in Urine	Electrocardiogram
1	8/ 1/34 12/11/34				9.6	3.6		240		38	11.3	4.48	6,400	78		1	1	9	18	3		
	10/14/38	6.2	3.6	2.6	8.6	3.2	5.6			2	14.5	4.49	6,240	76		3	0	6	12	3		Normal
2	6/ 9/36	7.1	2.6	4.8	11.1	3.8					12.1	4.90	4,420	63	8	3	0	16	10	0	+	Flat T wave in lead IV
3	12/ 3/36	7.50	3.17	1.33	9.6	3.7	5.7	133			11.5	5.340	5,340	57	11	5	2	18	7	0		Flat T wave in lead IV
	10/28/37	8.2	3.8	4.4	14.2	3.7		161		50	13.0	5.680	5,680	55	9	4	1	20	5	6		
					13.0	3.0	8.5				13.0	5.01	9,040	20	54	3	0	7	1	12		
	9/15/38	8.3	3.1	5.2	14.2	3.0	6.7						9,920	10	38	0	0	13	3	8	0	Prominent P wave in leads II and III W QRS in lead IV Inverted T wave in leads II and III Diphasic T wave in leads II and IV, inverted T wave in lead III
4	3/16/37										13.0		10,100	70	8	0	0	29	0	2		
	8/25/37	9.3	3.3	6.0	12.8	3.6					13.7	5.10	9,840	53	15	3	2	22	5	0		
	9/29/38	9.1	3.3	5.8	10.2	2.5	4.9			15	13.7		7,450								0	

dition had healed. Definite retention of bilirubin in the bilirubin tolerance test of Soffer¹¹ was found in the 4 instances in which it was studied. A substance resembling Bence Jones protein in its solubility at the boiling point was found in the urine in 2 cases, in both of which there were suggestive changes in the fingers. It was not present in the cases in which there were definite cysts. The only other urinary abnormality noted was an occasional trace of albumin.

TABLE 5—Summary

Date	Case 1		Case 2	Case 3		Case 4	Case 5	
	12/11/34	10/14/38		12/3/36	9/15/38		5/3/37	4/27/39
Lymph node								
Culture								
Aerobic	0			0	0		0	
Anaerobic				0	0		0	
Sabouraud	0			0	0		0	
Tubercle	0						0	
Other					+			
Inoculation								
Guinea pig	0			0	0		0	
Rabbit	0				0			
Mouse					0			
Rat								
Chicken					0			
Cutaneous tests								
Positive tuberculin				1 1000 2+		1 1000 1+		
Negative tuberculin	1 100	1 1000					1 100	1 1000
Frei				0			0	0
Sarcoid								
1, case 3				+		±	+	
2, case 7								0
3, case 11								
Monilia								1+
Blastomyces							0	1+
Brucella				0				
Blood serum								
Wassermann	0		0	0		0	0	
Kahn	0	0	0	0		0	0	
Monilia		0			0			0
Blastomyces	0	0						0
Other				Tularensis 0 Heterophil 0				
Sputum								
Smears								
Acid fast	0			0	0			
Fungi	Yeast			0	0			
Culture								
Bacteria	Friedlander			Staph aureus	Staph aureus			
Fungi	0			0	0			

Neither ova nor parasites were observed in the feces.

Electrocardiographic studies were made in 8 cases, with the finding of prominent P waves in 2 cases and flat or inverted T waves in 2 cases. No cardiac symptoms were observed, though the liver was enlarged in both cases in which the P waves were prominent.

Three grams of ascorbic acid by mouth was required by patient 10, and 2 Gm by patient 11, to saturate the body, as measured by colorimetric titration of the urine. This amount was in the range of the requirements of normal persons observed in the clinic. The test was repeated in four

¹¹ Soffer, L. J. Present Day Status of Liver Function Tests, *Medicine* **14** 185, 1935.

The basal metabolic rate was not elevated in cases 3 and 7

ETIOLOGIC STUDIES

Cutaneous tests with tuberculin were made in all but 2 cases, starting with dilutions of 1:100,000 and gradually increasing the dose. The Frei

of Ethnologic Studies

[illegible]

reaction was faintly positive for twenty-four hours in case 9, but it was negative five months later. Cutaneous tests with blastomyces filtrate 1:3 and with undiluted stock *Monilia albicans* vaccine were done; faintly positive reactions were occasionally observed in tests repeated later. An extract from a lymph node of patient 3, prepared according to the method of Williams and Nickelson,⁶ gave questionably positive reactions when injected into the skin of 3 patients, with absolutely negative results in 4 controls, 1 of which had active pulmonary tuberculosis.

(tests done by Dr C E Leach, Baltimore, December 1936 to July 1937) Extracts of nodes of patients 7 and 11, similarly prepared, each gave completely negative results in 4 patients, with questionably positive reactions in the patients from whose nodes they were made. It is possible that some variation in the technic of preparation of the second and third antigens was responsible for the different results, for with the short duration of the disease in the second instance it would seem logical that the infecting agent would be present in greater quantity and in a more virulent form than in the first and third specimens from patients in whom the disease was chronic.

Agglutination by the blood serum of *M. albicans* and complement fixation with blastomyces antigen were absent in 7 cases. Only patient 10, with a positive history of treated syphilis, and patient 9, with no history of syphilis, gave occasional positive serologic reactions for syphilis.

Examination of the sputum, when obtainable, gastric contents, nasal scrapings and urine in some cases failed to reveal acid-fast organisms. An unidentified budding fungus was seen in fresh unstained preparations once in the sputum of patient 1, but further search was futile. Direct smears of the removed lymph nodes in this case likewise gave negative results. Cultures of sputum for fungi were made in 4 cases, with uniformly negative results.

Specimens of excised lymph nodes were planted aerobically and anaerobically on blood agar at 37 C, on Sabouraud's medium at room temperature and occasionally on acid-fast mediums. In 3 instances cultures were planted on plain agar over benzene and petrolatum for soil bacteria. In case 3 a single yellow colony of pleomorphic gram-positive bacilli, some of which were partially acid-fast, was recovered, but the organism died out on subcultures before it could be identified. The colony and smears resembled in some respects the organism recovered from a patient with a condition resembling sarcoid by Mellon and Beinhauer¹². In patient 7 a small gram-negative coccobacillus was recovered but likewise died out before it was identified.

Inoculations of excised nodes gave uniformly negative results in guinea pigs, rabbits, chickens, mice and rats. With the exception of rabbits and chickens duplicate animals were inoculated. In the guinea pigs tuberculin tests were done on all and biucellergen tests on some before the animals were killed. No gross lesions were observed in any, occasional microscopic sections were made. I did not attempt to repeat the work of Schaumann, who reinjected the ground-up lymphoid material of the first into succeeding series of animals.

¹² Mellon, R. R., and Beinhauer, L. G. The Pathogenesis of Noncaseating Tuberculosis of the Skin and Lymph Glands, *Arch Dermat & Syph* **36** 515 (Sept) 1937.

TREATMENT

Treatment has been empiric. All the patients were advised to take a high calory, high vitamin diet, with cod liver oil and tomato or orange juice, to rest and to remain in the sunshine as much as possible. Three patients received ultraviolet irradiation, eight to ten exposures, which was gradually increased to eight minutes' duration, but there was no permanent improvement. One patient had received ultraviolet irradiation in another hospital without benefit. Roentgen ray therapy has been tried in 1 case, but sufficient time has not elapsed to evaluate it. Hyperpyrexia, induced by the intravenous administration of typhoid flagella antigen, caused no improvement in 1 case. Sodium gold thiosulfate given intravenously has been used sporadically with no noticeable benefit.

Intravenous injection of neoarsphenamine was credited by patient 5 with causing improvement. Other patients had received the drug before they were seen or have since received it in treatment of syphilis, with no benefit. Desensitization to Williams and Nickerson's antigen might be tried in patients who react positively on cutaneous test to it.

Iodides have been given without harm to 1 patient with lesions in the lungs. Several other patients who have similar roentgen appearances and similar chemical changes in the blood but have not had biopsies done and hence are not included in the series have been given iodides with no harm or benefit. The sputum was uniformly increased under iodides but remained negative for acid-fast organisms and fungi.

The recovery of Snapper's⁸ patient 3 coincided with the administration of ascorbic acid. The maintenance of the blood of the patients near saturation caused no immediate improvement.

COMMENT

The disease may be confused clinically with tuberculosis, Hodgkin's disease, lymphosarcoma, leukemia and fungous infections, the correct diagnosis is usually reached by exclusion. The condition in Negroes may run a short course, with marked lesions during the active stage, but completely clear up. The extent of the weight loss in the patients of this series is greater than would be expected from the experience of others. The occurrence of lesions in situated muscle, and in the tibia, ulna and ribs is uncommon. The unusual distribution of the enlarged lymph nodes and the involvement of the nares and eyelids tend to differentiate this disease from others. The chronicity and the low mortality rate indicate an etiologic agent of low virulence.

The sedimentation rate of the red blood cells cannot be used as an indicator of the activity of the disease process, for hyperglobulinemia increases the rate.¹³ The lymphocyte-monocyte ratio cannot be used for

¹³ Jeghers, H., and Selesnick, S. Hyperproteinemia. Its Significance. *Internat. Clin.* 3: 248, 1937.

prognosis, as in tuberculosis. The definite tendency toward neutropenia and leukopenia are consistent with (1) the observations on the blood in virus diseases, such as measles and the common cold (the absence of a demonstrable etiologic agent may point toward a virus as the cause of the disease) and (2) the absence of an allergic state (anergic phase) if the disease is tuberculous in origin. The constant observing of eosinophils in the blood, on the other hand, points toward an allergic state.

The chemical studies of the blood indicate no relation of the osseous lesions to hyperfunction of the parathyroid glands. The changes in the serum proteins may indicate activity in the lesions. From the similarity of the fractional precipitation curves of blood serum in these patients to those in patients with disease of the liver,¹⁴ the evidence of diminished excretory power of the liver, as shown by bilirubin tolerance tests, and the invasion and fibrosis of the liver observed in patients with sarcoid who came to autopsy,⁷ it appears that the liver is damaged to a greater extent than is usually recognized. The fractional precipitation curves of blood serum and the observing of substances resembling Bence Jones protein in the urine may indicate the formation of abnormal proteins.

The etiologic studies have elicited no new positive data. The use of rabbits, mice, rats and chickens, in addition to the usual guinea pigs, should make possible the recovery of atypical tubercle bacilli. The occasional faintly positive reactions of the skin to the tests with fungi are observed in many healthy persons. The failure to duplicate the results of Williams and Nickerson with cutaneous tests to an extract of tissue may be due to the use of lymph node in place of skin. The patient with the most marked cutaneous lesions gave irregularly positive serologic tests for syphilis and could not be used as a source for sarcoid antigen. The ability of the skin of the patients to react is indicated by the immediate appearance of wheal and erythema in response to all antigens exhibited by patients 5 and 7. It is possible that some unrecovered member of the general group of bacteria related to the actinomyces, the leprosy bacillus or the tubercle bacillus is the etiologic agent. The similarity of the bony and facial lesions to those of leprosy has been pointed out by other observers.¹⁵

The pathologic reaction is not specific for any group of bacteria. Similar epithelioid reactions can be elicited by tubercle bacilli, fungi or

14 Perlzweig, W. A., Kondritzer, A. A., and Bruch, E. The Solubility Precipitation Patterns of the Serum Proteins, *J. Biol. Chem.* **123**, 1938, unpublished data.

15 Murdock, J. R., and Hutter, H. J. Leprosy. A Roentgenological Survey, *Am. J. Roentgenol.* **28**, 598, 1932.

even inert substances, such as aluminum hydroxide,¹⁶ lecithin obtained from yeast and phosphatide or wax derivatives of tubercle bacilli¹⁷ or of blastomycetes¹⁸ Anergic tuberculosis and fungous diseases can be differentiated by cultural methods, animal inoculation and serologic tests The absence of polymorphonuclear leukocytes and of eosinophils in the tissues would indicate lack of an allergic response Allergy to fatty fractions of organisms has never been demonstrated in experimental animals, inoculations of lipids leave a residual eosinophilic response at the site¹⁹ No eosinophils have been present in the tissues of the patients in this series, but other observers have reported them Necrosis has been more prominent in this series than in others, this phenomenon usually occurs only in the presence of altered tissue reactivity (allergy) Why could not these patients be exhibiting an exaggerated response in the form of epithelioid cells to small amounts of a lipid fraction of a single organism or a variety of organisms, analogous to the necrosis, polymorphonuclear neutrophilic infiltration and edema of the familiar allergic response to proteins? The large mononuclear cell is the one which predominantly responds to lipids This theory could explain (1) the absence of positive cutaneous reactions (only protein materials have been used), (2) the failure to recover organisms from the lesions (only a few organisms or breakdown products would be necessary to evoke the response), (3) the occurrence of lesions in lymphoid tissue predominantly, where reticuloendothelial elements are plentiful, and (4) some cutaneous lesions as a reaction to the circulating lipid at a distance from the site of infection (analogous to the "id" reactions of the skin in tuberculosis and fungous diseases) Cutaneous tests to purified phosphatide and other lipid fractions of tubercle bacilli gave negative results in normal animals, with an altered response in tuberculous animals^{19b} Biopsies after injection of minute amounts of lipid into the skin of patients with sarcoid would aid in studying this point On the basis of present evidence, the conclusion is reached that the etiologic agent is still unknown

SUMMARY

Eleven patients with generalized sarcoid have been studied over a period of four years, including 2 who have been clinically well for two

16 Olitsky, P. K., and Harford, C. G. Intranuclear Inclusion Bodies in the Tissue Reactions Produced by Injections of Certain Foreign Substances, *Am J Path* **13**:729, 1937

17 Sabin, F. R., Doan, C. A., and Forkner, C. E. Studies on Tuberculosis, *J Exper Med*, 1930, supp 3, pp 1-152

18 Baker, R. D. Unpublished data

19 (a) Sabin, F. R., and Joyner, A. L. Tubercular Allergy Without Infection, *J Exper Med* **68** 659, 1938 (b) Smithburn, K. C., and Sabin, F. R. Reactions of Normal and Tuberculous Animals to Tuberculo-Protein and Tuberculo-Phosphatide, *ibid* **68** 641, 1938

years. The group is the second in which Negroes predominate and includes the first American Indian reported.

Definite changes in the content of calcium, protein and phosphatase of the blood were found. The phosphorus and nonprotein nitrogen were not altered. The cholesterol content was usually low or normal in cases in which the condition was active. Bilirubin tolerance tests showed retention. Calcium tolerance tests gave varied results. Substances resembling Bence Jones protein were occasionally present in the urine.

Etiologic studies, with emphasis on fungi and acid-fast bacilli, using animal inoculation, cultures and serologic and cutaneous tests, gave negative results. The cutaneous test suggested by Williams and Nickerson did not give positive results in our patients. The etiologic agent remains unknown.

Hematologic studies have confirmed low or normal white blood cell counts, neutropenia (without a shift to the left in the Schilling hemogram), eosinophilia, monocytosis and increased sedimentation rate. Occasional nonspecific changes were observed in the electrocardiogram.

The pathologic picture varied from that usually reported in the complete absence of eosinophils, the presence of moderate numbers of giant cells in acute lesions and the occasional presence of necrosis and amyloid.

No specific treatment has been discovered.

It is suggested that the reaction may be an exaggerated nonspecific response to a lipid fraction of varied organisms.

REPORT OF CASES

CASE 1—Uveoparotid fever for four months, military pulmonary involvement, moderate glandular swelling, acute lesions revealed by biopsy, duration two years, patient well for two years.

J. L., a married Negro farmer aged 26, was observed Aug. 1, 1934, complaining of swelling of the nodes in his neck of four months' duration. The family history was not significant. His wife had given birth to a stillborn child four years previously, a living child was born subsequently. His general health had been excellent except for smallpox at the age of 2 years, frequent epistaxes and frequent attacks of draining ears. Four years previously he had had marked painless swelling of the nodes of the neck for one week.

Four months previously he had noted generalized weakness, dyspnea and enlargement of the nodes of the neck, with remittent fever to 102 F. Painless nodules appeared under the skin over the arms and legs. He had some pain in the chest, and had raised small amounts of sputum in the morning. He had lost 27 pounds (12.2 Kg.). All the joints of the body had been stiff without swelling.

The temperature, pulse and respirations were normal. He was not ill but showed evidence of loss in weight. The skin was clear. All the lymph nodes of the body were enlarged, particularly those at the angle of the right jaw and in the inguinal region. Nodules were felt at the external canthus of the right eye. Paralysis of the sixth nerve on the left side was noted. Other nodules were felt in the muscles of the arms and legs. The tonsils were enlarged. The liver was palpable, the spleen was not felt.

A biopsy specimen of a muscle of the left arm showed epithelioid cells and occasional giant cells. Roentgenograms of the chest showed hilar nodes and small miliary areas in both lungs.

He was placed on a tuberculosis regimen, without improvement. On December 11 he was admitted to the hospital. New complaints included dull headaches, diplopia, polydipsia and polyuria, further loss of weight, 3 pounds (1.4 Kg), and enlargement of the parotid glands similar to a childhood attack of mumps. The nodules in the muscles had become the size of walnuts. Small ulcers appeared at the corners and on the roof of the mouth and on the arms and legs. The skin itched and the ulcers crusted. The wrists and elbows swelled.

A few crusted papules were noted near the mouth. The skin was dry and scaly. The parotid glands were markedly enlarged, as were all the peripheral lymph nodes, some measured 3 cm. A few dry rales were heard at the angle of the right scapula after coughing. Nodules were felt along the epididymis.

The temperature remained below 38 C (100.4 F) except for one rise to 38.4 C. Roentgenograms showed massive soft miliary spread of pulmonary lesions. Roentgenograms of the hands and long bones were normal. On examination of one specimen of sputum yeast cells and filaments were seen. Study of other specimens gave negative results, as did cultures. Biopsies of an epitrochlear node and a parotid gland showed epithelioid cells, with minimal necrosis but no fungi or bacteria. Cultures and inoculations of the nodes gave negative results. All serologic tests for fungi gave negative results.

The patient gained weight resting at home for twelve months. By June 1936, two years after onset, the swelling in the glands and nodes had disappeared, he felt perfectly well and resumed farming. When seen in October 1938, he appeared to be perfectly well. One postauricular node was palpable. Scars were present at the edges of the corneas. The lesion in the chest had entirely cleared except for minimal peribronchial thickening. The tuberculin test and serologic tests for fungi gave negative results.

CASE 2—Cutaneous lesions for twelve months, soft infiltration in the middle portion of the lung, decalcification of hands

R. P., a farm Negress aged 23, was observed June 9, 1936, complaining of a cutaneous eruption of twelve months' duration. The family history was not significant. She had been married three years, the first pregnancy resulted in a miscarriage, and two others, in children who died by the second day. Her general health was good. She had frequent sore throats in the winter. She contracted gonorrhea in 1935, with vaginal discharge and stiff swollen knees. The Wassermann reaction had been positive in January 1936, and she had received intravenous therapy twice weekly since.

Twelve months before admission she noted the appearance of papules in the skin, first on the eyelids and then on the face, legs and trunk. They were moderately tender to touch, did not itch and never disappeared. Six months previously a slight cough developed, productive of white sputum but not accompanied by fever. She had rare night sweats and nocturia (micturition twice nightly). She had lost 15 pounds (6.8 Kg).

The temperature, pulse and respirations were normal. She did not appear ill. In the skin were nontender papules without inflammation 5 mm in size. No lymph nodes were enlarged. The tonsils were large. The liver and spleen were not felt. The lungs were clear on auscultation. Roentgenograms of the lungs showed extensive soft infiltration, chiefly in the middle of the lung fields. Roentgenograms of the hands showed decalcification and early trabeculation. A biopsy of the skin showed typical hard tubercles.

The patient was placed on a tuberculosis regimen, with cod liver oil, milk and sunshine. She reported by letter twenty-seven months later that she was perhaps a little improved.

CASE 3—Generalized enlargement of lymph nodes for seven years, progressive involvement of bones, minimal cutaneous and pulmonary changes

F M, a farm Negress aged 27, was first observed Dec 12, 1936, complaining of pain in the hands and feet which had begun three years before. The family history was not significant. She was single, a pregnancy had ended in a miscarriage at three months. Her general health had been good before the present illness except for pneumonia at the age of 16 and frequent infections of the upper part of the respiratory tract since that time. Constipation with hemorrhoids and occasional periods of bloody diarrhea had been present for ten years. Vaginal discharge had been present for ten years, and the menses were irregular.

Eight years previously the patient had had a sudden onset of pain in the lower part of the abdomen on both sides, which was accentuated by the menses. Seven years previously she had noted gradual painless enlargement of the inguinal nodes. Three years previously aching in the knee joints with swelling and increased heat had begun. The feet, hands, arms and elbows were soon involved. Pain in the hands and feet persisted, and deformity of the phalanges and nails progressed to such a point that she could not use her hands or stand on her feet. Gradual painless involvement of all the nodes of the body ensued. For two years anorexia and nocturia had been present, with some dimness of vision and frontal headache. She had lost 30 pounds (13.6 Kg) since the onset of the illness, with a loss of 8 pounds (3.6 Kg) in the preceding two years. Ingestion of a patent medicine ten months previously had been followed by a generalized pustular eruption, most marked on the face, mouth and genitalia.

The temperature, pulse and respirations were normal. The patient appeared chronically ill. The skin was dry and scaling, with a few subcutaneous nodules over the cheeks, arms and legs. All the lymph nodes of the body were enlarged, particularly those along the borders of the pectoral, deltoid and arm muscles, they were rubbery and nontender. The nails of the fingers and toes were thickened and brittle, with longitudinal ridging of some, the terminal phalanges were misshapen. The tonsils were slightly enlarged and ragged. The lungs were clear. The liver and spleen were not felt. A single temperature reading above 38 C (100.4 F) was made.

Biopsy of the skin and a lymph node showed hard tubercles with rare giant cells. Roentgenograms of the hands and feet showed extensive trabeculation and cyst formation. Enlarged mediastinal nodes with slight peribronchial thickening were present. On a regimen of ultraviolet therapy in the hospital and exposure to sunshine, rest and ingestion of cod liver oil at home, the patient gained 6 pounds (2.7 Kg) and felt better than she had in two years. The pain in the joints decreased, and she was doing housework. The skin occasionally itched.

On her next admission, Oct 28, 1937, the inguinal and axillary nodes had increased in size, and the lacrimal glands were now enlarged. The scleras were clear. The liver was enlarged, the spleen was not felt. The second pulmonic sound was accentuated and split.

She was given twelve daily intravenous injections of typhoid vaccine, resulting in chills and fever. During this time stab forms of the polymorphonuclear leukocytes markedly increased, and the proportion of the various mononuclear cells varied markedly from day to day.

She continued her previous regimen at home and returned to the hospital on Sept 15, 1938. She had noticed no dyspnea, and the pains in the joints were improved. She was losing weight. The left tibia was sore and swelled intermittently, a cyst was demonstrated at this site by a roentgenogram. Pain was present along the right costal margin, and a slight cough productive of white sputum had developed. The skin showed only scars. The lymph nodes were increasing in size, the axillary nodes were painful. A detached nodule was present at the upper lateral border of the left lobe of the thyroid. Dry rubs without rales were heard over the chest. Roentgenograms of the chest showed no change since the previous examination. The cysts in the feet were increasing in size. A biopsy of a lymph node showed hyalinization of fibrous tissue, complete replacement by epithelioid cells and the presence of amyloid.

CASE 4—Marked involvement of the eyes for one year with complete healing in two years, gradual progressive enlargement of the lymph nodes, pulmonary symptoms with no demonstrable lesions in the lungs

A B, an American Indian farmer aged 22, was observed Feb 15, 1937, complaining of pain in the eyes of one year's duration. One grandfather had died of cancer. He had been married three years, his wife's only pregnancy resulted in a living child. His general health was good. He had frequent earaches, sore throats, epistaxes and nonproductive colds. For three years he had had epigastric pain between meals. He had had jaundice at the age of 6 years.

Twelve months previously infection in the upper part of the respiratory tract had developed, with headache and thick yellow discharge from the left nostril. For six months he had had a slight cough without sputum or fever. One week after onset dimness of vision with slight pain in the eyes began. A small amount of pus had been present for two weeks in one eye. At the onset the inguinal nodes became enlarged and tender, followed by nontender swelling of the other lymph nodes of the body. Soreness in the right hip and left elbow began. For two months anorexia and nausea had been present. He had lost 20 pounds (9.1 Kg).

The temperature was normal, but tachycardia was present, he did not appear ill. The skin was clear. All the lymph nodes of the body were enlarged up to 1.5 cm in size, including the preauricular, postauricular, submental and epitrochlear nodes and those near the pectoral and deltoid muscles and on the thigh. The conjunctivas were injected, and iridocyclitis and keratitis were present. The pupils were irregular and fixed. Pain was present over the bridge of the nose, and the septum was scaling but intact. The tonsils were small and slightly injected, the lungs were clear. The spleen was palpable.

Roentgenograms of the hands and feet were normal, and those of the chest showed slight hilar thickening and enlarged glands.

A biopsy of a lymph node near the deltoid muscle showed hard tubercles and no organisms. The lymphoid tissue was entirely replaced by the epithelioid reaction.

He was admitted to the hospital on March 16, 1937. He was afebrile, but the pulse rate remained 100 to 120. He received ultraviolet radiation for ten days and then was sent home to continue treatment with cod liver oil and sun baths. In the course of the next four months the eyes cleared, but he gained no weight and showed no general improvement.

He returned to the hospital on Sept 26, 1938. He had lost 3 pounds (1.4 Kg), but was working daily on the farm. The inguinal nodes were sore, and the others were slowly increasing in size. Pain developed under the sternum, with a cough productive of $\frac{1}{2}$ cup of greenish yellow sputum daily, but there was no

fever Aching was noted in the right hip and knee He had taken a pint (475 cc) of cod liver oil weekly for three weeks A swollen node had developed in his baby's neck, but the child was not available for examination

The temperature was 38.4 C (101.1 F), pulse rate 120 and the respiratory rate 32, but the patient did not appear acutely ill The nodes were enlarged, rubbery, freely movable and nontender and measured up to 2 by 3 cm The skin was clear The eye showed scars only Moist scales were present in the left maxillary line The liver and spleen were not felt

Roentgenograms of the chest showed enlargement of the hilar nodes with no infiltration of the central portion of the lungs

CASE 5—Painful enlargement of the lymph nodes for two months, duration six months, patient well for two years

J C, a Negro lumber truck driver aged 27, was admitted to the hospital on May 7, 1937, complaining of tender swollen nodes in the neck and groin which had been noticeable for two months The family history was not significant He had been married for eight years and had four living children His general health was excellent He had had smallpox and malaria in childhood He had frequent colds and sore throats

Two months previously the patient had contracted an infection of the upper part of the respiratory tract, which was followed by gradual painful enlargement of the nodes at the angle of the jaw Generalized enlargement of the lymph nodes soon followed, with moderate pain in the inguinal nodes Headache was troublesome He noted some epigastric pain, with occasional nausea and diarrhea He lost 20 pounds (9.1 Kg)

The temperature, pulse and respirations were normal He was not ill The skin was clear The lymph nodes were all enlarged, soft or rubbery, discrete and slightly tender The largest, 6 cm in size, were in the inguinal region The epitrochlear nodes measured 3 cm The popliteal nodes were palpable The lungs were clear The liver and spleen were not felt The tonsils were pale and not enlarged

Roentgenograms of the hands were normal, the mediastinal nodes were enlarged, but the lungs were clear except for hilar thickening Biopsies of cervical and epitrochlear lymph nodes showed marked epithelioid reaction, with rare giant cells and minimal necrosis He was afebrile and was sent home to receive weekly intravenous injections of 0.45 Gm of neoarsphenamine After the tenth injection the nodes disappeared, and he felt perfectly well, he received fifteen injections in all

He returned to the hospital April 27, 1939 He had worked every day since leaving and had gained 20 pounds (9.1 Kg) For the preceding four weeks he had noted pain below the right scapula and in the axilla, accompanied by slight cough productive in the mornings of small amounts of yellow sputum The nodes had entirely disappeared except for small submandibular ones Several pale papules measuring 3 mm were present on the skin of the face and chest The cutaneous tests gave markedly positive reactions to all antigens at thirty minutes, with wheal and reticulated erythema, but the reactions all disappeared in twenty-four hours Roentgenograms of the hands and feet were normal The mediastinal nodes had disappeared, and only slight peribronchial thickening was present

CASE 6—Generalized enlargement of the lymph nodes for eighteen months, cutaneous lesions, asymptomatic pulmonary involvement

J T, an unmarried Negro yard boy aged 21, was observed June 16, 1937, complaining of a cutaneous eruption of one year's duration The family history was not

significant Eighteen months previously small round papules appeared on the penis and the surrounding skin, followed by similar lesions on the buttocks and swelling of the inguinal nodes One year previously moderately tender lesions appeared around the mouth, nose and back of the neck The application of salves to the penis was beneficial, but the facial lesions spread No pus was present Wassermann reactions were repeatedly negative, and intravenous antisyphilitic therapy caused no improvement

The temperature, pulse and respirations were normal Firm smooth papules without inflammation were present on the neck, face and eyelids Flat circinate irregular lesions were present at the corners of the mouth and on the anterior nares The cervical, auricular, axillary, inguinal and femoral nodes were enlarged, firm, rubbery, nontender and discrete The lungs were clear on physical examination

Biopsies of the skin, the lip and a posterior cervical lymph node showed epithelioid cells, no organisms and scattered brown pigment Roentgenograms of the chest showed minimal infiltration in the central portion of the lung, peribronchial fibrosis and enlargement of the lymph nodes Attempts to trace this patient have been futile

CASE 7—Swelling of the lymph nodes for ten weeks, minimal peribronchial thickening, questionable trabeculation of the toes, healing

M P, an unmarried Negro domestic servant aged 27, was admitted to the hospital June 14, 1938, complaining of swelling of the nodes of the neck which had begun ten weeks before The family history was not significant Her general health had been excellent Six months before admission she began to lose weight and to fatigue easily Ten weeks before admission she noted slowly growing nontender nodules in the neck, under the chin, in the armpits and in the groin Anorexia had been marked She had had no fever The skin had turned noticeably darker and the hair began to fall out She lost 25 pounds (11.3 Kg)

The temperature, pulse and respirations were normal She was not ill The skin was clear The cervical, submental, epitrochlear, axillary, inguinal and pectoral nodes were enlarged, discrete and not tender The eyes were clear The tonsils were small The liver was at the costal margin, the spleen was not felt The lungs were clear The temperature remained 38 C (100.4 F) or below until a biopsy specimen was taken, when it reached 39.4 C (102.92 F) for two days A cervical node was excised and found adherent to the surrounding tissues Sections showed hard tubercles, hyalinization of connective tissue and no organisms The tonsils were removed, but sections were not made of them Roentgenograms of the chest showed a few hilar nodes

On a tuberculosis regimen at home the patient gained 9 pounds (4.1 Kg) Vague pain developed in the lower part of the abdomen On October 17 an inguinal node measuring 2.5 by 1.5 cm was excised The sections showed a similar process to that in the other node A single colony of a gram-negative coccobacillus was grown on anaerobic blood agar Roentgenograms of the hands were normal The hilar nodes were slightly enlarged, and minimal peribronchial thickening was present

She returned to the hospital May 18, 1939, one year after onset, complaining of pain under the right scapula during the past winter She had had no fever at home, had gained 16 pounds (7.3 Kg) and appeared quite well Some aching had been present in the muscles of the right thigh The skin and eyes were clear Postauricular, submaxillary and small cervical, axillary and inguinal nodes were present On deep inspiration the liver descended 2 fingerbreadths and the spleen 1 fingerbreadth below the costal margin

Roentgenograms of the toes showed questionable trabeculation. The hilar nodes had receded slightly, the peribronchial thickening was unchanged. Biopsy of another lymph node showed more definite tubercles with more giant cells and slight necrosis. Fat cells were scattered throughout. Cutaneous tests gave immediate reactions to all antigens, with wheals and erythema at thirty minutes, but the reactions disappeared in twenty-four hours.

CASE 8—Generalized enlargement of the lymph nodes for four months, soft infiltration in the middle of the lungs, questionable cysts of fingers

G. B., a white farmer aged 36, was admitted to the hospital Aug. 16, 1938, because of loss of weight for four months. The family history was not significant. He had been married twice, the first wife dying in childbirth. His general health had been good except for an attack of pain in many of the joints accompanied by swelling at the age of 14. He had been examined in the orthopedic clinic in 1935 because of pain in the lower part of the back after an injury. Roentgenograms of the spine had been normal. He had had no enlargement of the lymph nodes or cutaneous nodules at that time but showed signs of mitral stenosis. The liver and spleen were not palpable.

About one year before the patient's admission gradual malaise had begun, followed by the loss of 40 pounds (18.1 Kg.) in the preceding five months. Four months previously he had noted gradual enlargement of all the lymph nodes of the body. One month later a small mass appeared in the epigastrium. He had no fever. The skin did not itch. His libido had decreased. Burning on urination and nocturia had been present for one year.

The temperature, pulse and respirations were normal. He appeared chronically ill. A few nodules were felt in the skin over the back. All the lymph nodes of the body were enlarged, with the largest 4 by 3 cm. in the right supraclavicular fossa. The eyes were clear. The tonsils were slightly enlarged and reddened. The lungs were clear on physical examination. The heart showed no change since the previous examination. The liver was palpable 3 cm. and the spleen 2 cm. below the costal margins. In the right upper quadrant and near the umbilicus were firm nontender masses measuring 5 cm., which were thought to be enlarged intra-abdominal lymph nodes. Large external hemorrhoids were present. The fingers showed rounded tips.

Gastrointestinal roentgenograms were normal. Roentgenograms of the chest showed no enlargement of the mediastinal nodes but soft infiltration in the middle part of the lung fields. Questionable cysts and trabeculation were present in the finger tips. Roentgenograms of the feet were normal. Biopsy of a lymph node showed almost complete replacement of lymphoid tissue by round collections of epithelioid cells, and the intervening connective tissue showed slight hyalinization. Minimal necrosis was present. The patient left before studies were completed and has not been heard from since.

CASE 9—Extensive cutaneous lesions for six years, asymptomatic military fibrotic lesions of the lungs

B. M., a Negro school teacher aged 32, was observed Nov. 7, 1938, complaining of a cutaneous eruption of six years' duration. Several cousins had asthma. She had been married ten years, the only pregnancy resulted in a living child. Her general health had been excellent. She had had smallpox at the age of 9 years.

Six years previously nonitching lesions had appeared on the upper lip and spread to the nose, arms and neck and then to the skin in general, including the genitalia. She received a course of ultraviolet irradiation in 1931 and one hundred intravenous injections of arsenicals in 1933, without improvement.

The temperature and the respirations were normal, and she did not appear ill. Tachycardia (heart rate 100) was present. The skin of the entire body, including the scalp, eyelids, nares, labia and perineum, was covered with raised, nonscaling, linear or cuniculate lesions. They were not tender or anesthetic. The palms and soles were not involved. A lipoma was present on the left wrist. The nasal septum was intact. No enlarged lymph nodes were felt. The tonsils were atrophied. The lungs were clear on physical examination. The liver and the spleen were not palpable.

Biopsy of the skin of the abdomen showed minimal invasion of the corium and well formed hard tubercles, with rare giant cells and no necrosis. Roentgenograms of the chest showed miliary fine fibrotic areas, with slightly enlarged nodes. Tiny questionable cysts were observed in the fingers.

CASE 10—Lesion of left eye for ten years (syphilitic or sarcoid?), enlargement of the lymph nodes for seven years, chronic pulmonary disease without acid-fast organisms or fungi

L. B., an unmarried Negro waiter aged 30, was observed Feb. 24, 1939, complaining of a cough of three years' duration. His father had died of diabetes. The patient's general health had been good except that he had had pneumonia at the age of 13. Frequent sore throats were terminated by a tonsillectomy in 1933. He worked as a plasterer's helper for two years.

Ten years previously pain had developed in the patient's left eye. Seven years previously a penile lesion had developed and had been followed by enlargement of the inguinal and postauricular nodes. Syphilitic uinitis was diagnosed, and he had received continuous treatment for one year without improvement. An uidectomy had been performed, resulting in complete loss of sight in that eye. Three years before admission progressive shortness of breath had begun, accompanied by a cough productive of yellow sputum, which progressed in one year to the point of incapacitating him for work. He had frequent attacks of pain in the chest, with no fever or hemoptysis. No cutaneous rash or persistent enlargement of the lymph nodes had been present. He had lost 25 pounds (11.3 Kg.) since the onset and 10 pounds (4.5 Kg.) in the past year.

The temperature, pulse and respirations on admission were normal. He did not appear ill. The skin was clear. There was moderate general enlargement of the lymph nodes, including the cervical and epitrochlear nodes. The right pupil was irregular and eccentrically placed, but it reacted to light. The conjunctiva of the left eye was hyperemic, the cornea was opaque, and there was a wedge-shaped scar in the upper portion of the iris. Motion of the left side of the chest was limited, and the percussion note was dull there. Coarse moist rales were present between the scapulas, more marked on the left. The fingers showed slight clubbing. The liver and spleen were not felt.

Biopsy of an inguinal lymph node showed scattered small hard tubercles. Only marked reticuloendothelial hyperplasia was found in an axillary node. The temperature ranged below 37.5 C (99.5 F) except for one rise to 38 C (100.4 F). Roentgenograms of the chest showed diffuse infiltration of the central portion of both lung fields, the ribs showed suspicious areas of rarefaction. The diaphragm was deformed by adhesions. The mediastinal nodes were slightly enlarged.

CASE 11—Marked cutaneous lesions for five years, generalized enlargement of the lymph nodes, massive asymptomatic lesions of the lungs, minimal bone involvement

J. F., a Negro tobacco worker aged 30, was seen April 4, 1939, complaining of an eruption on the face which had begun five years before. Two sisters had been

stillborn His wife had died of a ruptured appendix, one child was living and well His general health was excellent, although he had frequent infections of the upper part of the respiratory tract

Five years before admission the patient had noticed several vesicles on his forehead, followed by weeping nontender papules on the bridge of the nose, which had spread to the cheeks, nares and eyelids The neck, genitalia and perineum were involved three years later A roentgenogram of the chest taken three weeks before admission, after influenza, showed extensive lesions in the lungs He had had no fever or cough and had lost no weight He had received iodides without harm

The temperature, pulse and respirations were normal, and he was not ill Over the face was a butterfly distribution of a papular eruption which was also observed on the neck, legs, scrotum, penis and anus Some areas were crater-like and measured 2 cm Two ulcers were seen on the roof of the mouth The cervical, axillary, epitrochlear and femoral nodes were firm, discrete, enlarged and not tender The tonsils were small and not infected A few moist rales were present over both lungs The liver and spleen were not felt Biopsy of the skin showed tubercles, with occasional giant cells and minimal central necrosis The epithelium was ulcerated, but no polymorphonuclear reaction was present The lymph node showed many hard tubercles, with rare giant cells and no necrosis The connective tissue was markedly hyalinized, and amyloid was present No organisms were found Roentgenograms of the fingers and toes showed trabeculation, with a cyst in a cuneiform bone Roentgenograms of the chest showed extensive fibrosis, chiefly in the middle parts of the lungs, and the diaphragm was markedly deformed The mediastinal nodes were slightly enlarged

CRITERIA FOR THE CLASSIFICATION AND DIAGNOSIS OF PERIPHERAL VAS- CULAR DISEASES

GAMLIEL SALAND, M D

CHARLES KLEIN, M D

HERMAN ZURROW, M D

ABRAHAM GOOTNICK, M D

AND

ABRAHAM KATZ, M D

NEW YORK

The study of peripheral vascular diseases has made rapid strides in the past decade, and has now reached the stage at which it can benefit from a clear, concise and descriptive classification. The need for such a classification becomes obvious when an attempt is made to cull the literature or to abstract hospital records. Increasing interest in peripheral vascular diseases has led to rapid accumulation of new knowledge, and the multiplicity of investigative reports has sharpened the need for some degree of uniformity in clinical designation.

Repeatedly, methods of treatment reported to have yielded excellent results are subsequently found to be of no value in other hands. The reason too often is that widely differing stages of a disease process are grouped together as an entity, and cases included in one classification in one clinic are called instances of something else in another clinic.

The simplest and most practical method of classification, we feel, must be one which enforces a complete study of each case reported, which leaves little to conjecture and which is flexible enough to allow still undiscovered factors to be included at a later date. The set of diagnostic criteria here presented is planned for a threefold use: (1) In the individual case it offers a workable means for accurately defining the patient's initial status, (2) it offers a means of determining his progress and (3) uniform diagnostic standards make possible valid comparisons of data from many sources, and permit crystallization of prognostic and therapeutic principles from these data.

Our scheme is patterned after the diagnostic criteria for heart disease published by the Heart Committee of the New York Tuberculosis and

From the Department of Peripheral Vascular Diseases, the Bronx Hospital

Health Association¹ No claim is made that these criteria are ultimate and immutable principles They are intended as a uniform basis for diagnosis, subject to such modification as time and use may indicate

A comprehensive diagnosis of peripheral vascular disease should include a statement of (A) the etiologic agent or agents, (B) the anatomic status, (C) the extent of physiologic impairment, and (D) the functional capacity of the patient

A ETIOLOGIC AGENTS IN PERIPHERAL VASCULAR DISEASES

I Acrocyanosis—The characteristic signs and symptoms of acrocyanosis² may be summarized as follows

- (a) The condition occurs predominantly in young women
- (b) The involvement is usually bilateral, though it may be unilateral
- (c) The usual site of involvement is the fingers, or the hands up to the wrists
- (d) Pain is absent
- (e) Changes in color do not occur with changes in posture
- (f) Exposure to cold produces spasm, low skin temperature and cyanosis of the extremities
- (g) Heat or warmth produces rubor and normal skin temperature
- (h) The arterial pulsations are normal
- (i) Gangrene never occurs
- (j) Oscillometric measurement shows normal expansion with arterial pulsation in the involved area
- (k) Vasodilatation tests show normal rises in skin temperature
- (l) Arteriographic examination shows normal filling of vessels
- (m) Microscopic examination of the capillaries during the cyanotic phase may show spasm of the arterioles and dilated venous branches

The condition may be differentiated from Raynaud's syndrome by the absence of asphyctic changes in color, of pain, even during the cyanotic phase, and of gangrene It may be distinguished from thromboangitis obliterans and arteriosclerosis obliterans by the absence of organic changes in both vessels and tissues

II Arteriosclerosis Obliterans—The characteristics of arteriosclerosis obliterans³ may be noted in the following manner

- (a) The disease usually occurs in persons over 50 years of age

1 Criteria for the Classification and Diagnosis of Heart Disease, ed 3, New York Tuberculosis and Health Association, 1932

2 (a) Lewis, T Vascular Disorders of the Limbs, New York, The Macmillan Company, 1936 (b) Elliot, A H, Evans, R D, and Stone, C S Acrocyanosis A Study of the Circulatory Fault, Am Heart J **11** 431, 1936

3 Hines, E A, Jr Thrombo-Arteriosclerosis Obliterans, Proc Staff Meet, Mayo Clin **13** 694, 1938 Lewis^{2a}

(b) The sex ratio in the patients with this disease shows that men predominate over women, 6 to 1

(c) Race is of no significance as an etiologic factor

(d) The lower extremities are the chief site of involvement, in only about 1 per cent of the cases are symptoms noted in the upper extremities

(e) The chief complaint at the onset is usually intermittent claudication. In the later stages, rest pain may occur as a result of either ischemic neuritis or local changes in tissue, also, paresthesias may be noted. Patients may complain of excessive coldness of the limbs

(f) Any degree of tissue degeneration up to ulceration and gangrene may develop

(g) Physical examination usually reveals a cold extremity, flushed when dependent and pallid when elevated, in which there are varying degrees of degeneration of tissue

(h) Pulsations in any or all vessels may be diminished or absent

(i) Oscillometric tracings show diminished to absent pulsations of the limbs

(j) Vasodilatation tests do not produce normal rises in skin temperature

(k) Arteriographic examination shows varying degrees of organic obstruction

(l) Roentgenographic evidence of calcification of vessels is common, but it is not an index of vascular occlusion

III Arteriovenous Fistula—The signs and symptoms of arteriovenous fistula⁴ are both local and systemic. The local symptoms may be described as follows

(a) The involvement is most frequently unilateral

(b) The mass of the fistula is usually evident

(c) Bruit and thrill over the mass are continuous

(d) There is high venous pressure in the affected extremity, as a result of this there may occur (1) enlargement of the limb, (2) increased warmth of the limb or (3) recurrent transient edema

(e) Arterial pulsation is diminished below the lesion

(f) Oscillometric readings are high above the lesion and low beneath it

(g) There is increased oxygen tension in the venous return from the limb

⁴ Hitzig, W. M., and Master, A. M. Arteriovenous Fistula, *J. Mt. Sinai Hosp.* 1: 269, 1935

The systemic phenomena depend on many features—for example, the size of the fistula, the caliber of the vessels involved, the duration of the lesion and its distance from the heart, the age and the activity of the patient, and the presence or absence of coexisting cardiovascular disease. The systemic phenomena may be minimal or may include the signs of advanced cardiac failure. The severity of the signs in the following list will vary with the degree of cardiac compensation.

(a) The circulation time (arm to tongue) is usually increased, even with normal venous pressure.

(b) The venous pressure is unchanged in the compensated phase, in the later stages, when right ventricular failure occurs, it is of course elevated.

(c) The systolic arterial pressure is high, the diastolic, low.

(d) The pulse rate is elevated. The production of bradycardia on compression of the mass is almost pathognomonic.

Arteriographic examination, when feasible, will usually establish the diagnosis if arteriovenous fistula is present.

IV Autohemagglutination—This condition⁵ presents vascular symptoms without evidence of vascular pathologic change. A reversible autohemagglutination, which occurs on cooling and disappears on warming, can be demonstrated. In the cooling-agglutination phase, intravascular plugging with the agglutinated cells occurs.

The demonstration of the Donath-Landsteiner phenomenon—that is, autohemolysis—is not necessary, however, for diagnostic purposes. In vitro, agglutination occurs at 10 C in titers up to 1:1,000, but it does not occur in any concentration at 37 C.

V Diseases of the Central Nervous System—All peripheral vascular changes which develop as a result of syringomyelia, poliomyelitis and hemiplegia have this in common: they are essentially changes due to disuse.⁶ Loss of function in a limb causes diminished circulation of blood in that limb, in proportion as the demands of muscular activity diminish.^{2a} Curtailment of blood supply brings on, in turn, the varying signs of malnutrition of the skin that have been called “trophic changes”: coldness and cyanosis of the affected limb, development of atrophy and edema and an excessive susceptibility to cold and physical

⁵ McCombs, R. P., and McElroy, J. S. Reversible Autohemagglutination with Peripheral Vascular Symptoms, *Arch Int Med* **59** 107 (Jan.) 1937.

⁶ (a) Allen, E. V., and Craig, W. M. Effect of Lesions of the Central Nervous System on the Circulation, *Proc Staff Meet, Mayo Clin* **13** 131, 1938. (b) Lewis, T., and Pickering, G. W. Circulatory Changes in the Fingers in Some Diseases of the Nervous System, *Clin Sc* **2** 149, 1936. (c) Kerr, W. J., and Underwood, F. J. Hemoconstriction of the Vascular System Associated with Cerebral Disease, *Am Heart J* **12** 713, 1936.

trauma, which often result in indolent "trophic" ulcers. In all these states the absence of organic obliterative disease can be confirmed by the fact that eliminating the vasotonic influence of the sympathetic nerve supply results in complete vasodilatation in the limb.

The distinguishing characteristics of these conditions are therefore

(a) Prolonged loss of muscular function in the limb or limbs affected, associated with the history and signs of disease of the central nervous system

(b) Varying degrees of coldness and cyanosis, and changes resulting from nutritional deficiencies, in the affected as compared with the unaffected limbs

(c) Capacity of the vessels in the affected limbs to dilate completely on removal of the sympathetic vasotonic control in those areas

Brain lesions which involve the vasomotor centers in the region of the hypothalamus occasionally cause vasoconstriction on the side of the body opposite the lesion^{6c}. The limbs affected are cold and pale or cold and cyanotic. Pulsations in these limbs are absent or greatly diminished, and there is no vasodilatation in response to measures that abolish sympathetic tone.

Cord tumors that exert pressure on the lateral columns have been known to cause marked peripheral vasoconstriction, the distribution corresponding to the site of the central lesion.

VI Cervical Rib Syndrome—The symptoms in this syndrome depend on distortion of the course of the subclavian artery and the distal trunk of the brachial plexus. This distortion may be caused by an anomalous cervical rib or a fibrous band, or by tension at the insertion of the scalenus anticus muscle sufficient to elevate the arch of these structures.⁷ In the majority of cases the symptoms are neurologic only, occasionally there is associated vascular involvement. Symptoms usually appear after adolescence.

The neurologic manifestations are

(a) Pain in the deltoid region, shoulder and upper part of the arm. There may be radiation to the back of the neck and head, to the seventh cervical spine or to the ulnar aspect of the hand and arm.

(b) Tenderness over the insertion of the scalenus anticus muscle behind the clavicular attachment of the sternomastoid.

(c) Relief on inclining the head toward the affected shoulder.

(d) Sensory impairment, and later atrophy, along the ulnar side of the hand and forearm (as a result of involvement of nerve fibers originating in the eighth cervical or first dorsal root).

⁷ Callander, C. L. *Surgical Anatomy*, Philadelphia, W. B. Saunders Company, 1939. Craig, W. M., and Horton, B. T. *Diagnosis and Treatment of Vascular Disorders of the Extremities*, S. Clin. North America **18**:899, 1938.

Vascular manifestations

(a) The commonest changes are secondary to pressure on a nerve and are a result of disuse. The limb is colder than its fellow, it may show mild cyanosis and, occasionally, edema. (Stimulation of sympathetic nerve fibers in the brachial plexus, with resulting vasospasm, may be a factor in these changes.) There is no impairment of peripheral pulsation in these cases, and the limb responds normally to vasodilating stimuli.

(b) Major vascular changes are rare and are caused by embolism from a thrombus at the site of pressure. The effects vary, depending on the size and location of the embolus, from transient coldness and cyanosis of the digits to gangrene of the finger tips.

Roentgenographic examination will demonstrate an anomalous cervical rib when it is present. More often than not, however, this anomaly is absent, and the diagnosis must rest on clinical recognition of the neurovascular syndrome.

VII Exposure to Cold—Apart from its etiologic role in peripheral vascular disease, prolonged intense cold acts as a noxious physical agent on the outlying structures of persons with normal vascular trees, and produces frostbite.

The effect of cold on peripheral vascular tone is twofold:

1. Directly, it brings about vasoconstriction in an exposed limb, and consequent diminution in the volume of blood circulating in that limb.
2. Indirectly, by way of the central nervous system, it causes vasoconstriction of cutaneous vessels, generally in a reflex manner. In normal persons, the sum of these two effects will not ordinarily suffice to arrest completely the circulation to a limb,^{2a} but in persons with impaired peripheral vessels this may happen temporarily and reversibly, as in milder forms of Raynaud's disease during the asphyctic phase, or permanently, with resulting tissue death, in more advanced grades of obliterative vascular involvement. An episode of exposure to cold may be the determining factor in the transition from a state of vascular insufficiency still consistent with viability of the tissues to total obliteration of vessels, with development of gangrene.

In some of the so-called functional vascular disorders (acrocyanosis, erythrocyanosis) cold must be classed as the exciting etiologic factor, the predisposing cause being local change in the vessels which renders them excessively sensitive to cold.

VIII Diabetes Mellitus—The role of diabetes mellitus in peripheral vascular disease is not that of a direct etiologic agent. Although the disease is not the cause of arteriosclerosis obliterans, it may hasten

the onset of the latter. Thus it has been estimated⁹ that pulsation in one or more of the peripheral vessels is absent ten to twenty years earlier in diabetic than in nondiabetic persons. The importance of diabetes mellitus, then, is in modifying adversely the course of the arteriosclerotic process, especially when infection or trauma supervenes.

IX. Embolism and Thrombosis—Embolism and thrombosis are acute vascular accidents which lead to a dramatic train of tissue change. Differentiation between embolic and thrombotic obstruction of a peripheral artery depends not on the state of the limb affected but rather on associated findings more or less remote from the site of obstruction. The factors to be evaluated are:

(a) The presence or absence of a possible source of emboli. The commonest cause is pathologic change in the left side of the heart, the conditions associated with emboli in systemic arteries are mitral stenosis, auricular fibrillation (especially during changes from fibrillation to regular sinus rhythm), congestive heart failure, bacterial endocarditis involving the aortic or mitral valve and coronary thrombosis with infarction of the left ventricle and formation of mural thrombus.

(b) The age of the patient. Thrombosis is more commonly the cause of sudden occlusion in old than in young persons. A history of claudication, or other manifestation of previous vascular impairment in the limb also is in favor of the diagnosis of thrombosis rather than embolism.

(c) Simultaneous bilateral occlusion is most often embolic in nature, especially if the level of occlusion is below the bifurcation of the aorta. In unilateral occlusions the vascular status in the opposite limb is a diagnostic help, the presence of vascular obliterative disease favoring the possibility of thrombosis.

In a limb which has suffered an occlusive accident, the characteristic vascular change is loss of the pulse distal to the occlusion. Moreover, the insult to the vessel wall at the point of occlusion tends to induce spasm of the vessel for a varying length proximal to the occlusion, as well as spasm of neighboring vessels. The changes in the tissue are the result of sudden profound curtailment of the blood supply, and are an exaggeration of the milder, more gradual ischemia of chronic obliterative disease. These changes vary, in accordance with the degree of impairment of the blood flow. Thus, occlusion of a common iliac artery causes prostrating pain, anesthesia, paralysis, blanching and coldness of the entire limb and rapid development of gangrene, while occlusion below the popliteal artery may cause few or no symptoms.

8 Footnote deleted

9 Olmsted, W. H. Arteriosclerosis of the Lower Extremities in Diabetes Mellitus, *Internat. Clin.* 1:195, 1936.

and may result in nothing more than loss of pulsation in the anterior or posterior tibial artery. The maintenance of viability in the limb depends on

(a) The caliber of the vessel blocked. Other things being equal, the nearer the occlusion is to the aorta the greater the likelihood of gangrene.

(b) The presence of adequate collateral circulation. Occlusion of an artery in a young person calls into play expansile healthy collateral vessels, which may reroute enough blood to save the limb. Thrombosis in an elderly patient must be compensated for by collateral vessels, which may themselves be in an advanced stage of obliterative arteriosclerosis.

(c) Extension of the clot. Either thrombus or embolus may serve as a nucleus for a propagating thrombus, which may extend for a considerable length in an artery and may occlude the mouths of collateral vessels.

X Endocrine Dysfunction—In people passing through periods of endocrine imbalance, such as young girls with menstrual difficulties and women undergoing severe menopausal disorders, vasospastic phenomena may develop. The peripheral vascular manifestations may involve the upper or lower extremities and tend to be symmetric. Numbness, subjective coldness and paresthesias are the commonest complaints. Objectively, the limbs are cold to the touch and may exhibit a cyanotic tinge. But there are neither the episodes of transient asphyctic color changes nor the evidences of impaired tissue nutrition. All the pulses are normally palpable when the limb is warm, there is no pallor on elevation or rubrocyanosis on dependency of the limbs, and there is normal response to vasodilating stimuli.

Psychoneurosis affects the peripheral arterial tree in the same manner as endocrine dysfunction. Here too, the complaints occur predominantly in women, and are results of a sympathicotonia of central origin. The clinical manifestations are those described in the section on endocrine imbalance.

*XI Ergotism*¹⁰—The incidence of ergotism at present is almost entirely confined to women of fertile age, their histories revealing prolonged use of ergot during the puerperium or for control of uterine bleeding. Recent widespread use of ergot products for the relief of migraine has apparently not been attended by instances of vascular damage. Outstanding findings are as follows

10 von Storch, T. J. C. Complications Following the Use of Ergotamine Tartrate. Their Relation to Treatment of Migraine Headache, *J. A. M. A.* **111**: 293 (July 23) 1938.

(a) The lower limbs are affected earlier and more often than the upper

(b) Impairment is symmetric

(c) The symptoms progress from tingling and cramps to coldness and numbness. There are pallor and marbling of the skin, diminution of peripheral pulsations, subnormal or absent oscillometric readings. In later stages there is inadequate response to vasodilating stimuli.

(d) Gangrene, which develops gradually when the disease is severe, is dry and symmetric, and the parts separate by mummification.

(e) The systemic blood pressure is frequently elevated.

*XII Erythrocyanosis*¹¹—In the differential diagnosis of erythrocyanosis the following points are noted:

(a) The disease occurs usually in young and middle-aged women.

(b) Uniform or mottled reddish blue discoloration of the skin in the lower half of the legs is characteristic.

(c) Involvement is bilateral and does not extend distal to the malleoli.

(d) The affected skin feels cold to the touch and dimples on pressure.

(e) The circumference of the leg is increased by subcutaneous infiltration of fat, and there may be indurated nodules in the tissue.

(f) Arterial pulsation is normal, and the vasodilatation response is normal.

*XIII Erythromelalgia*¹²—The characteristic signs and symptoms of erythromelalgia may be summarized as follows:

(a) It is a disorder chiefly of the lower extremities, marked by a paroxysmal throbbing and burning pain in the skin, and accompanied by a dusky mottled redness of the parts.

(b) Pain is induced by warmth and dependency and is relieved by cooling and elevation.

(c) The skin temperature of the extremity at which distress occurs is constant for the individual patient.

(d) Bounding pulses are present, there is no evidence of obliterative arterial disease.

11 Telford, E. D., and Simmons, H. T. Erythrocyanosis, *Brit. M. J.* **1**:629, 1936.

12 (a) Smith, L. A., and Allen, E. V. Erythromelalgia (Erythromelalgia) of the Extremities, *Am. Heart J.* **16**:175, 1938. (b) Mufson, I. Clinical Observations in Erythromelalgia and a Method for Its Symptomatic Relief, *ibid.* **13**:483, 1937. (c) Lowenthal, L. J. A. Erythromelalgia in East African Native, *East African M. J.* **11**:397, 1935.

(e) Microscopic observation of the capillaries shows that the venules, which appear bright red, are increased in number and enlarged to five times the normal size

XIV Phlebitis—This condition may produce arterial lesions both directly and indirectly¹³ A true periaarterial and even arterial inflammation may be set up in the proximity of a phlebotic vessel¹⁴ Phlebitis may simulate acute arterial occlusion because of spasm of the main arteries of the affected extremity The spasm is reflex and is mediated through the sympathetic nervous system The differential diagnosis is based on relaxation of the spasm by vasodilators, chemical, physical, or both

*XV Polycythemia*¹⁵—The peripheral vascular findings in polycythemia are

(a) A blue-red discoloration of the skin, observed as deep raspberry red

(b) Increased sensitiveness to cold

(c) Paresthesias of the extremities

(d) Susceptibility to phlebitis, thrombosis and gangrene of the toes

(e) Engorged and distended capillaries

XVI Raynaud's Disease and Raynaud's Phenomenon—The original criteria postulated by Raynaud¹⁶ in 1888 were

(a) Episodes of change in color of the vasospastic type, excited by cold and emotion

(b) Symmetric involvement

(c) Predominance in young women

(d) Normal pulsations in palpable vessels

(e) Absence of extensive gangrene, or its limitation to minimal grades in cutaneous areas

13 Homans, J Thrombophlebitis in Legs, New England J Med **218** 594, 1938

14 Samuels, S S The Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York, Oxford University Press, 1936 Lewis^{2a}

15 (a) Harrop, G A, Jr Polycythemia, Medicine **7** 291, 1928 (b) Weber, F P, and Bode, O B Polycythaemia, Erythrocytosis, and Erythraemia (Vaquez-Osler Syndrome) An Epitome Based on Parkes Weber's Book of 1921 and the Recent Literature of the Subject, London, H K Lewis & Company, 1929 (c) Norman, I L, and Allen, E V Vascular Complications of Polycythemia, Am Heart J **13** 257, 1937

16 Raynaud, A G M On Local Asphyxia and Symmetrical Gangrene of the Extremities, translated by T Barlow, in Selected Monographs, London, New Sydenham Society, 1888

To these Allen and Brown¹⁷ have added

- (f) Absence of any disease that may be causal
- (g) Symptoms of at least two years' duration
- (h) Absence of obliterative arterial disease proved by
 - (1) Absence of gangrene
 - (2) Normal oscillometric readings
 - (3) Normal vasodilatation tests

(i) Characteristic changes in the capillary bed at margins of the nails

True Raynaud's disease is rare (it has been seen once in 4,000 admissions to the Mayo Clinic). More common is Raynaud's phenomenon, which has been defined by Lewis,^{2a} Pickering¹⁸ and Hunt¹⁹ as active and intermittent closure of small arteries, the size of the digital arteries, supplying the extremities, the clinical signs are discoloration of the affected parts, which become waxy or fully cyanotic and are often numb, and their fall in temperature to room temperature.

Raynaud's phenomenon¹⁹ may occur in

- (a) Normal persons exposed to low temperatures long enough to lower the temperature of the blood
- (b) Persons with "hereditary cold fingers"
- (c) Patients who have had a local injury to the hands or feet, and workers who use vibrating tools
- (d) Persons with thromboangitis obliterans
- (e) Persons with arteriosclerosis obliterans
- (f) Persons with syphilitic arteritis
- (g) Persons with "rheumatic arteritis"
- (h) Persons with the scalenus anticus syndrome
- (i) Persons with advanced pulmonary tuberculosis, leukemia, polycythemia, lupus erythematosus, chronic malaria, chronic arsenical poisoning, osteoporosis or paroxysmal hemoglobinuria

XVII Scleroderma—This disease is usually considered in association with Raynaud's disease, to which it may be a sequel. Two theories are in vogue as to its causation. One holds that intermittent spasm of the digital arteries or those of similar size constitutes the original state, and that this leads to atrophy and fibrosis of the tissues supplied by the vessels. The other is that diffuse scleroderma arises from a primary

17 Allen, E. V., and Brown, G. E. Raynaud's Disease Affecting Men, *Ann Int Med* 5:1384, 1932.

18 Pickering, G. W. On Clinical Recognition of Structural Disease of Peripheral Vessels, *Brit M J* 2:1106, 1933.

19 Hunt, J. H. The Raynaud Phenomena. A Critical Review, *Quart J Med* 5:399, 1936.

disturbance, infectious or toxic, in the skin and subcutaneous tissue, leading to a state of subacute or chronic inflammation, and that fibrous changes in tissue or vessels are secondary to the inflammation ²¹

This disease affects young women, although it is rare in female children ²⁰ It is usually preceded by asphyctic color changes in the affected areas Sclerodactylia is present, but swelling is also present Necrosis, when it occurs, is superficial Pigmentation of the affected regions is common, as are arthritic changes both of the atrophic and of the hypertrophic type The objective signs and tests are those of obliterative arterial disease

XVIII Thromboangitis Obliterans ²¹—This disease may occur in all races and in all climates Ninety-nine per cent of the patients are males The age incidence is from 15 to 45 years, but study of pathologic specimens has been strongly suggestive of the possibility of its association, at least, with arteriosclerosis in aged persons It is recognizably inflammatory and, although its infectious nature is not established, isolated instances of its transmission from patient to operating surgeon have been recorded ²² Comprehensive statistical studies seem to indicate that although smoking may in many cases aggravate the disease, it in itself does not produce the condition The disease is chronic, with many acute exacerbations and long periods of remission In a large proportion of the cases some degree of involvement of the vessels of the upper extremity is present The veins are not immune, superficial phlebitis is characteristic of the disease Obliterative vascular phenomena are responsible for the symptoms, of which intermittent claudication is usually the presenting complaint Pain while at rest may be severe and out of proportion to the evident ischemia, changes in the tissues are common, and, as mentioned before, superficial migrating phlebitis is present in 30 per cent of the patients

A diagnosis may be made on the basis of the following criteria

- (a) Age young adult, 15 to 45 years old
- (b) Sex male in 99 per cent of the cases
- (c) Evidence of obliterative vascular disease—that is, intermittent claudication, pallor, rubor and absence of pulses
- (d) Presence of superficial phlebitis
- (e) Chronicity
- (f) Results of pathologic examination

²⁰ Wright, I S, and Duryee, A W Treatment of Scleroderma with Mecholyli Iontophoresis, *Am Heart J* **14** 603, 1937

²¹ Hines, E A, Jr Thrombo-Arteriosclerosis Obliterans A Clinical Study of Two Hundred and Eighty Cases, *Proc Staff Meet, Mayo Clin* **13** 694, 1938

²² Allen, E V, and Lauderdale, T L Accidental Transmission of Thromboangitis Obliterans from Man to Man, *Proc Staff Meet, Mayo Clin* **11** 641, 1936

B ANATOMIC STATUS OF VESSELS AND TISSUES

At first glance, the separation of observations of anatomic status into those concerned with vessels and those concerned with tissue may appear artificial. Consideration, however, will show that such separation is absolutely necessary. Diagnostic efforts in the study of vascular diseases are directed toward an evaluation of the nature of the actual pathologic process present in the vessels and the extent of that process. All the clinical and laboratory tests are designed to give information as to the status of the vessels involved. The changes in the tissue are the end result of the vascular impairment, and help to guide the physician in recognizing progress or lack of progress during or after treatment. Many of these changes are, moreover, due to external causes, such as infection and trauma, which modify the result of the treatment.

For purposes of record, comparison and determination of progress we have set arbitrary, but sharply defined, criteria for the varying degrees of vascular involvement. In this way only can the statement "Degree of vascular obliteration 2 plus" have any significance when one examines a patient a year after the original admission, or when one compares cases with those reported elsewhere. Grading of the disease process in the limb as a whole is arrived at after a comprehensive evaluation of the following factors or observations:

I Vascular Anatomic Status—Changes in the anatomic status of the blood vessels may be classified as follows:

(a) *Pallor and rubrocyanosis*. Pallor may be demonstrated in a limb with impaired circulation by elevating the limb to an angle of 45 to 60 degrees for two minutes, with the patient supine. Under these conditions, the degree and rate of development of pallor are an index of ischemia in the limb. The effect of gravity may be augmented by having the patient alternately flex and extend the foot at the ankle, the muscular contractions helping to expel the venous blood which might otherwise color the skin. The pallor is usually most striking over the sole. In this test the rapid onset (within a few seconds) of cadaverous pallor is graded 4 plus. Slight pallor at the end of the two minute period is graded 1 plus.

To demonstrate rubrocyanosis, the limb is allowed to hang down, free and relaxed, for a maximum of two minutes. Prompt onset of an intense reddish purple discoloration in the toes or foot is a maximal (4 plus) reaction. Absence of appreciable rubrocyanosis at the end of the two minute period constitutes a normal response and is graded zero.

The conditions for both procedures are an environmental temperature of 25 to 28 C (77 to 82.4 F) and a preliminary rest period of at least thirty minutes in the horizontal position.

In this test, what we observe directly is only the status of the cutaneous capillaries and subpapillary venules, only by inference do we estimate the state of circulation in the part. Pallor is the resultant effect of arterial deficiency plus gravity. Rubriocyanosis is caused by the engorgement of dilated venules and capillaries with blood, with marked slowing of the blood flow and excessive deoxygenation.

(b) Palpation of pulses. The extremities to be examined should be warm. When the pulsation is but faintly felt it is advisable to take the precaution of checking with the patient's or the examiner's heart rate.

In the lower extremity the pulsation of the dorsalis pedis, anterior tibial, posterior tibial, popliteal and femoral arteries should be searched for. In the upper extremity the pulsations of the radial, ulnar, brachial, and axillary arteries should be examined.

In this examination, minimal grading (0) corresponds to the absence of pulsation of a vessel. From this base, the intensity of pulsation is graded upward from faint (1 plus), to full (4 plus).

(c) Temperature of the extremities by palpation. The back of the fingers may be used to evaluate differences in temperature, the results are graded as warm, cool or cold.

(d) Oscillometric measurement. This is a mechanical method for measuring the total expansion of a limb, at a given level, with each arterial pulsation. Its value rests chiefly on the fact that it records these pulsations graphically, and thus provides a permanent record for noting progress and for comparison. In our experience, it is not essential for diagnosis, nor may it be uniformly relied on to gauge peripheral vascular status. For example, it is by no means rare for a patient to improve clinically and physiologically while showing a simultaneous steady decrease in oscillometric readings.

Under ideal conditions, a recording oscillometer should be used, but it should be understood that standards of normal must be established for each individual oscillometer. These normal readings then correspond to the maximal (4 plus) grade in our scheme, while the absence of pulsation is grade 0. As in the palpation of pulses, basic conditions must be established, including a preliminary rest period, supine posture and sufficient heat to insure fully warm extremities. In cases of impending or actual gangrene or of acute vascular accident, oscillometric observations should not be made, to avoid further trauma from pressure.

(e) Roentgenographic examination. Both roentgenography and arteriography have been called on for aid in diagnosis.

(1) Demonstration of calcification in a vessel by roentgenography does not necessarily signify vascular obliterative disease, although it may be used as an index of degenerative change in the vessel wall. The atherosclerotic process which eventually leads to vascular occlusion and

obliteration may for a long time consist only of intimal and subintimal changes, which are not demonstrable by roentgenography

(2) Arteriography, on the other hand, enables one to demonstrate the actual circulatory pattern of a limb. It does not always differentiate spasm from organic obstruction. For a complete description of methods and evaluation of results in arteriography, the reader is referred to special discussions of the subject²³

(f) Capillary microscopy. The use of capillary microscopy as a means of demonstrating the presence of organic vascular change is still unreliable as a diagnostic procedure.

II Anatomic Status of Tissues—Changes in the anatomic status of the tissues may be classified as follows:

(a) No changes

(b) Trophic changes without lesions, evidenced by deformed, dry and brittle nails. The skin may be dry and flaky and may show marbling. The veins are collapsed if no varicosities exist. There is absence of hair growth. Muscular atrophy exists, and roentgenologic examination may reveal bony atrophy.

(c) Infections, classified as

1 Dermatomyositis

2 Cellulitis

3 Lymphangitis

4 Phlebitis

5 Ulceration, (1) superficial or (11) deep

(d) Gangrene

1 Following infection

2 Followed by infection

(e) Loss of members

C. PHYSIOLOGIC CHANGES

The physiologic changes refer mainly to three factors, intermittent claudication, spasm and vascular reserve.

I Intermittent Claudication—The pain of intermittent claudication is exercise pain. This is symptomatic, and its appearance varies with the rapidity and force of muscular contractions. It comes on more readily in cold than in warm weather.

The time it takes for the pain to appear is called claudication time. This can be measured by an ergometer, or simply in terms of the

23 (a) Bird, C. E. The Use in Arteriography of Substitutes for Colloidal Thorium Dioxide, *J. A. M. A.* **109** 1626 (Nov 13) 1937. (b) Yater, W. M. Thorotrast Arteriography of the Extremities, *Am. Heart J.* **12** 383, 1936. (c) Allen, E. V. How Arteries Compensate for Occlusion, *Arch. Int. Med.* **57** 601 (March) 1936.

distance, in blocks, that a person can walk before the pain sets in. Claudication pain never occurs on rest, and this fact differentiates it from arthritic and neuritic pain. Whatever the physiologic basis for this pain may be, it is evidently the result of an insufficient blood supply to the muscle in activity.

In our clinic we grade claudication time from 0 when the patient can walk unlimited distances without pain to 4 plus, when he cannot walk more than one half of a city block without the onset of pain. Absence of claudication pain does not guarantee adequacy of circulation, as the patient may be prevented from walking by other disease, such as angina pectoris.

II Spasm—Spasm of blood vessels is a factor of importance in both the organic and the functional diseases of the peripheral vascular tree. In the so-called functional group, in which no organic involvement is demonstrable, spasm alone is responsible for the clinical manifestations. This group includes acrocyanosis, erythrocyanosis, certain involvements of the central nervous system, anterior poliomyelitis, syringomyelia, some tumors of the brain and spinal cord, vasomotor imbalance of endocrine or psychoneurotic origin and early stages of ergotism and Raynaud's disease.

In the organic vascular diseases, spasm of varying degree is an associated factor. The problem here is to determine how much of the circulatory inadequacy is due to spasm and how much to organic involvement. It is well known that spasm may simulate all the clinical manifestations of acute or chronic obliterative disease. To estimate the presence or absence of spasm we apply the vasodilatation tests described in the following section.

III Vascular Reserve—Vascular reserve represents the maximal capacity of a limb for blood circulation. Determination of vascular reserve is the most important single objective in the study of the patient. It is a measure of the degree of vascular involvement, and it is an indication of how much we may hope to attain with suitable therapy. Periodic determination of vascular reserve is useful also as a means of following changes in the vascular status of the patient's limbs.

All tests at present available for the estimation of vascular reserve are based on the capacity for peripheral vasodilatation. In order of physiologic efficiency, the vasodilatation tests are spinal anesthesia, general anesthesia, peripheral nerve block, paravertebral block, the thermal reflex vasodilatation test and intravenous injection of typhoid vaccine. Tests involving estimation of histamine flare, saline wheal absorption, oxygen saturation of the blood, venous filling and intravenous injection of sodium nitrite are not in common use, and are not essential for diag-

nosis In our clinic we have found the thermal reflex vasodilatation test ²⁴ and the peripheral nerve block ²⁵ both feasible and dependable

The thermal test has its basis in the fact that when the blood has been warmed peripherally reflex generalized vasodilatation is induced when it reaches the medullary heat-regulating centers, as a mechanism for dissipating the excess heat This release of vasoconstrictor influence results in increased blood flow to the limbs, and may be estimated by measuring the changes in skin temperature

The test is performed as follows After a period of exposure, during which the limbs to be tested reach a constant temperature, the limbs not being tested are immersed in water at 108 to 112 F, and the upper part of the body is wrapped in a blanket Temperature readings are then taken for thirty minutes from the dorsal aspect of the terminal phalanx of the toes or fingers of the exposed limbs

The reflex paralysis of vasoconstriction is, of course, incapable of affecting organic narrowing of vessels, incomplete vasodilating response is thus indicative of organic obliterative change in the vessels When inadequate vasodilatation is observed in the reflex vasodilatation test, the results are checked by the direct method of peripheral nerve block

This test involves direct blocking of vasoconstrictor impulses to the medium-sized and small arteries In the upper extremity the ulnar or median nerves are blocked, in the lower extremity the posterior tibial and the common peroneal nerves A 1 per cent solution of procaine hydrochloride (without epinephrine) is infiltrated about the nerve, the block is then tested by checking the development of anesthesia or paralysis along the area of distribution of the nerve

In both the reflex vasodilatation and the nerve block tests, the rise of skin temperature to 30.5 C (86.9 F) in the toes or to 32 C (89.6 F) in the fingers is considered a normal response and is graded 4 plus Complete failure of the skin temperature to rise above the starting level, even after peripheral block, denotes far advanced impairment of the vascular reserve and is graded 0

24 (a) Gibbon, J. H., Jr., and Landis, E. M. Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J. Clin. Investigation* **11**:1019, 1932 (b) Landis, E. M., and Gibbon, J. H., Jr. A Simple Method of Producing Vasodilatation in the Lower Extremities, with Reference to Its Usefulness in Studies of Peripheral Vascular Disease, *Arch. Int. Med.* **52**:785 (Nov.) 1933 (c) Saland, G., Klein, C., and Zurrow, H. The Thermal Reflex Vasodilatation Test in Peripheral Vascular Disease, *Am. Heart J.* **17**:581, 1939

25 Scott, W. J. M., and Morton, J. J. Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, *J. A. M. A.* **97**:1212 (Oct. 24) 1931

D FUNCTIONAL CAPACITY OF PATIENT

Patients are grouped in four classes, according to their functional capacity

Class I Patients who have organic disease without symptoms

Class II Patients who have organic disease (*a*) with minimal symptoms or (*b*) with moderate symptoms

Class III Patients who have organic disease and are bedridden because of severe pain at rest, gangrene or infection

Class IV Patients who have symptoms without organic disease, "functional" group

SUMMARY

The classification of a case of peripheral vascular disease may be outlined as follows

A Etiologic Agents

B Anatomic status

I Vascular

II Tissue

C Physiologic status

I Claudication

II Spasm

III Vascular reserve

D Functional status

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1939

ASHTON GRAYBIEL, M D

WITH THE EDITORIAL ASSISTANCE OF PAUL D WHITE, M D

BOSTON

A survey of the literature on cardiovascular disease for the year 1939 reveals much that is of interest and importance. The most notable contributions are in regard to congenital heart disease, essential hypertension and the treatment of subacute bacterial endocarditis. Consequently, these subjects have been reviewed in considerable detail.

ELECTROCARDIOGRAPHIC STUDIES

It has long been known that an electrocardiogram similar to that for the adult can be obtained for the embryo at a very early age. With the improvement in amplifying apparatus, electrocardiographic features regarded as characteristic of adults have become recognizable in the electrocardiograms of progressively younger embryos. The studies carried out by Hoff and his associates¹ are interesting in that these investigators were able to secure records from the time that the heart beat of the chick embryo was just commencing through the period of rapid anatomic change leading to the establishment of the fundamental regional divisions of the heart. They found the earliest visible manifestations of cardiac activity in embryos of 29 to 30 hours and obtained the first consistent records when the embryos were 30 to 36 hours old (fifteen somite chick). At this stage the tubular heart is nearly straight and consists almost entirely of ventricle. The electrical record takes the form of a curve which first drops below, then rises above, the isoelectric line. Slightly older embryos (sixteen to seventeen somites) yield records showing a sharp downward deflection, followed by a rapid return to, or above, the baseline, which probably represents the QRS complex. Shortly thereafter the P wave appears, and by the fourth day of development the electrocardiogram has assumed substantially its adult configuration. Thus the authors were able to trace the appearance of all

From the Cardiac Clinic of the Massachusetts General Hospital

1 Hoff, E C, Kramer, T C, DuBois, D, and Patten, B M. The Development of the Electrocardiogram of the Embryonic Heart, *Am Heart J* **17** 470, 1939

the major features of the adult electrocardiogram in hearts so young that they lacked completely either a nerve supply or a specialized sinoventricular conduction system

Ashman and Hidden,² as a result of their electrocardiographic studies, have become convinced that the electrical axis of the T wave is of more significance than mere amplitude of the T wave expressed in millimeters. To test this theory, they selected at random several hundred electrocardiograms. Those tracings showing intraventricular block, or inversion of the T waves in lead I were eliminated, as were nearly all those showing inversion of the T waves in lead III. For each remaining electrocardiogram the average QRS axis and the ratio of the height of T_1 to the height of T_3 were determined. This ratio is a convenient way of expressing the electrical axis of the T wave. When their results were plotted on a diagram, it was found that the ratio T_1/T_3 is normally smaller the more the average electrical axis inclines to the right, and vice versa. A line was drawn in the diagram separating the normal from the abnormal T wave axes at different QRS axes. The decision as to whether or not a given T wave axis is abnormal depends on the average electrical axis of the QRS complex. It was found that in heart disease a rightward deviation of the electrical axis of the T wave is a common finding. An exception to the general rule is seen when the S waves are prominent, especially in leads II and III.

A number of authors³ have continued the study of the chest leads in electrocardiograms. The variations in normal persons are being carefully worked out, and also the abnormalities observed in various

2 Ashman, R, and Hidden, E H. Rightward Deviation of the Axis of the T-Wave as an Index of Myocardial Disease, *Ann Int Med* **12** 1682, 1939

3 Robinson, R W, Contratto, A W, and Levine, S A. The Precordial Lead I Findings for Patients with Normal Hearts and Those with Heart Disease Other Than Myocardial Infarction, *Arch Int Med* **63** 711 (April) 1939. Contratto, A W, Robinson, R W, and Levine, S A. The Precordial Lead II Findings for Patients with Myocardial Infarction, *ibid* **63** 732 (April) 1939. Vander Veer, J B, and Edwards, J C. The Significance of Small and Absent Initial Positive Deflections in the Chest Lead, *Am J M Sc* **197** 663, 1939. Stewart, H J, and Bailey, R L. The Effect of Posture on the Form of Precordial Leads of the Electrocardiogram, *Am Heart J* **18** 271, 1939. Geiger, A J. A Comparative Study of Precordial Leads IV R and IV F, *ibid* **18** 715, 1939. Wood, P, and Selzer, A. Chest Leads in Clinical Electrocardiography, *Brit Heart J* **1** 49, 1939. Kossmann, C E, and de la Chapelle, C E. The Precordial Electrocardiogram in Myocardial Infarction. II. Observations on Cases of Infarction of the Posterior Wall of the Left Ventricle, *Am Heart J* **18** 344, 1939. III. Observations on Cases in Which the Lesions Were Diffuse, *ibid* **18** 352, 1939. Mortensen V. Analysis of the QRS Complex in Precordial Leads in Cases of Anterior Wall Infarction, *Nord med (Hospitalstid)* **3** 2749, 1939. Evans, C. Changes in the Chest Lead Electrocardiogram in Coronary Thrombosis, *Brit Heart J* **1** 161, 1939

types of heart disease and in other disease states. In general, the findings are similar to those previously reviewed.⁴

Only a few years ago inversion or marked lowering of the T waves in leads I or II of the electrocardiogram was nearly always regarded as evidence of coronary heart disease. Gradually there has accumulated a list of exceptions to this rule, which has now reached such proportions that there is danger of underestimating its significance. Barker and his associates⁵ have shown that marked lowering of the T waves may occur as a result of overventilation (alkalosis) and that acidosis is accompanied by an increase in the amplitude of T. Thomson⁶ studied the effect of potassium salts on the form of the electrocardiogram and found that in general the administration of potassium salts was followed by an increase in the height of the T waves. Mainzer and Krause⁷ believe that they have found that fear may cause inversion of the T waves and alterations in the form of the ST segments.

ROENTGENOLOGIC STUDIES

Laubry and his associates⁸ have published an excellent atlas, beautifully illustrated, on the roentgen examination of the heart and great vessels. This work includes the many important studies made in the authors' clinic over a period of ten years. The teleroentgenography and roentgenokymography of the normal heart and aorta are illustrated in great detail, after which consideration is given to the various etiologic types of heart disease.

There has been continued interest in the determination of heart size by means of the roentgen ray.⁹ Of particular interest is the report of

4 Graybiel, A., and White, P. D. Diseases of the Heart. A Review of Significant Contributions Made During 1937, *Arch. Int. Med.* **61**: 808 (May) 1938, A Review of Significant Contributions Made During 1938, *ibid.* **63**: 980 (May) 1939.

5 Barker, P. S., Shrader, E. L., and Ronzoni, E. The Effects of Alkalosis and of Acidosis upon the Human Electrocardiogram, *Am. Heart J.* **17**: 169, 1939.

6 Thomson, W. A. R. Potassium and the T-Wave of the Electrocardiogram, *Lancet* **1**: 808, 1939, Effect of Potassium on the Heart in Man, *Brit. Heart J.* **1**: 269, 1939.

7 Mainzer, F., and Krause, M. Changes of the Electrocardiogram Brought About by Fear, *Cardiologia* **3**: 286, 1939.

8 Laubry, C., Cottenot, P., Routier, D., and Heim de Balsac, R. *Radiologie clinique du coeur et des gros vaisseaux*, Paris, Masson & Cie, 1939.

9 Jonsell, S. A Method for the Determination of the Heart Size by Teleroentgenography (A Heart Volume Index), *Acta radiol.* **20**: 325, 1939. Comeau, W. J., and White, P. D. An Evaluation of Heart Volume Determinations by the Rohrer-Kahlstorf Formula as a Clinical Method of Measuring Heart Size, *Am. Heart J.* **17**: 158, 1939. Hodges, F. J. Determination of Heart Size, *Am. J.*

Jonsell, who describes a method of determining heart volume based on the Rohrer-Kahlstorf formula. Teleroentgenograms are taken simultaneously in two directions at right angles, at a predetermined moment of the heart cycle, with the aid of a cathode ray oscillograph. Jonsell also describes a simplification of the method whereby the heart size is more easily determined and without the use of special apparatus.

Robb and Steinberg¹⁰ have added to their previous studies on the visualization of the chambers of the heart and great vessels by means of the radiopaque solution diodrast. Although this method must still be considered as being in an experimental stage, the results are indeed impressive. The value of their procedure is excellently illustrated in the study of a patient with cor pulmonale.

Routier and Heim de Balsac¹¹ made careful roentgenologic studies of the modifications of the trachea and bronchi associated with various types of heart disease. They review and extend some of their previous observations, showing that the left auricle as it enlarges meets the tracheal bifurcation, into which it penetrates like a wedge. "The two bronchi, being thus forced apart, curve in upon the auricular cap like a rider's legs gripping his horse." This widening of the angle of the tracheal bifurcation may reach nearly 180 degrees (normally 50 to 80 degrees), and the bronchi may be considerably constricted. The authors describe the anatomic relationship between the air passages and the pulmonary arterial tree in normal persons and in patients with various types of heart disease. When the pulmonary arteries are dilated, the bronchi, having to support abnormal weights, are drawn together so that the angle of the tracheal bifurcation becomes more acute. In extreme cases the caliber of the bronchi, especially that of the left, is reduced.

Roentgenol **42** 1, 1939. Terrill, E. H. Determination of the Cardiac Area. Simple Substitutes for the Two-Meter Film, the Orthodiagraph, and the Planimeter in Application of the Hodges-Eyster Formulae, *ibid* **42** 611, 1939. Ungerleider, H. E., and Clark, C. P. A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on the Teleroentgenogram, *Am Heart J* **17** 92, 1939. Kuttner, A. G., and Reyersbach, G. The Value of Special Radiologic Procedures in Detecting Cardiac Enlargement in Children with Rheumatic Heart Disease, *ibid* **18** 213, 1939.

10 Robb, G. P., and Steinberg, I. Visualization of the Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Heart Disease, *Am J Roentgenol* **42** 14, 1939, Visualization of the Chambers of the Heart and the Thoracic Blood Vessels in Pulmonary Heart Disease. A Case Study, *Ann Int Med* **13** 12, 1939.

11 Routier, D., and Heim de Balsac, R. Tracheal and Bronchial Modifications During the Course of Certain Cardiopathies Affecting the Pulmonary Artery, *Brit J Radiol* **12** 150, 1939.

CONGENITAL HEART DISEASE

Patent Ductus Arteriosus—The ductus arteriosus is a vascular channel connecting the pulmonary artery and the aorta. In the fetus the blood pumped into the pulmonary artery is shunted through the ductus into the aorta, the lungs being nonfunctioning. At birth the ductus normally closes in the manner so well shown by Barcroft and his associates. Rarely there is a failure of closure and the ductus remains patent throughout life. This is the third most common congenital cardiovascular abnormality. After birth, of course, the flow of blood in the ductus is from the aorta to the pulmonary artery. The added burden thus placed on the heart is directly proportional to the volume of shunted blood. This burden is often sufficient to produce congestive failure and death at an early age. Furthermore, subacute bacterial endarteritis develops as a complication in about one fourth of the cases, with death as a nearly inevitable consequence.

The possibility of ligating or otherwise obliterating the patent ductus has long been considered and even attempted, but last year the first successful ligation in man was reported by Gross and Hubbard¹². The patient was a girl 7½ years of age, who bore the operation very well and who recovered uneventfully in a short time.

Gross¹³ describes the operative procedure which he successfully used in 4 cases. An incision is made through the third left intercostal space from the sternum to the midaxillary line, and the rib above is divided at the costochondral junction. Opening the pleural cavity allows the lung to collapse, and an appropriate incision in the pleural covering of the mediastinum leads directly to the ductus arteriosus. The diameter of the ductus has little bearing on the possibility of ligating it, but the length is important, if the length is 0.5 cm. or more, it can be easily ligated.

Hubbard and his associates¹⁴ have critically evaluated the indications for surgical ligation of a patent ductus arteriosus. It is their opinion that retardation of growth, peripheral signs of an arteriovenous shunt of considerable magnitude or evidence of cardiac insufficiency are the important indications for operation. They rightly point out that while ligation of a patent ductus may lessen or remove the danger of

12 Gross, R. E., and Hubbard, J. P. Surgical Ligation of a Patent Ductus Arteriosus. Report of First Successful Case, *J. A. M. A.* **112**: 729 (Feb. 25) 1939.

13 Gross, R. E. A Surgical Approach for Ligation of a Patent Ductus Arteriosus, *New England J. Med.* **220**: 510, 1939.

14 Hubbard, J. P., Emerson, P. W., and Green, H. Indications for the Surgical Ligation of a Patent Ductus Arteriosus, *New England J. Med.* **221**: 481, 1939.

subacute bacterial endarteritis, there is no definite proof of this. The optimum age for operation would seem to be in childhood before the second decade, when the incidence of subacute bacterial endarteritis increases, and after the period of infancy.

Congenital "Aneurysmal" Dilatation of the Left Auricle—Semans and Taussig¹⁵ describe an enormous saccular dilatation of the left auricle in a 5 year old child. It is thought to have been due to a congenital abnormality either in the blood supply of the affected area or in the auricular myocardium. The authors reviewed the pertinent literature but were unable to find any record of a saccular dilatation of the left auricle that was believed to have been due to a congenital abnormality.

RHEUMATIC HEART DISEASE

Causes—The etiologic factors of rheumatic fever remain unknown. A preliminary report¹⁶ describing a pleuropneumonia-like organism obtained from rheumatic exudates has not been substantiated.

Eagles and Bradley,¹⁷ in their latest report, present good evidence that a specific virus is not present in the lesions of rheumatic fever. They were unable to confirm the observation that rheumatic exudates yield "elementary bodies" on centrifugation which are specifically agglutinated by the serum of patients with active rheumatic fever. They obtained just as many positive agglutinations with serum from patients with nonrheumatic arthritis as with serum from patients with rheumatic fever. Furthermore, in cases of rheumatic fever there was not found to be any relationship between the positive agglutination test and the clinical activity of the disease.

Coburn and Pauli¹⁸ have demonstrated secondary antigens and antibodies in patients with rheumatic fever. Reference should be made to the original article for the details of their theory and experiments.

Laboratory Tests—One of the most difficult and important problems arising from the treatment of patients with rheumatic heart disease is that of determining whether or not active rheumatic infection is present. Much help is derived, in the solution of this problem, from a study of the white blood cells and a determination of the red blood cell sedimentation rate. More accurate standards than have heretofore been avail-

15 Semans, J. H., and Taussig, H. B. Congenital "Aneurysmal" Dilatation of the Left Auricle, *Bull. Johns Hopkins Hosp.* **63** 404, 1938.

16 Swift, H. F., and Brown, T. M. Pathogenic Pleuropneumonia-like Microorganisms from Acute Rheumatic Exudates and Tissues, *Science* **89** 271, 1939.

17 Eagles, G. H., and Bradley, W. H. The Agglutination of Suspensions of Virus-like Particles Prepared from Exudates in Acute Rheumatic Fever, *Quart. J. Med.* **8** 173, 1939.

18 Coburn, A. F., and Pauli, R. H. Precipitinogen in Serum Prior to Onset of Acute Rheumatism, *J. Exper. Med.* **69** 143, 1939.

able have been published by Osgood and his corps of workers¹⁹ They determined the total, differential and absolute leukocyte counts and sedimentation rates of healthy persons in four age groups, namely, 4 to 7, 8 to 14, 15 to 18, and 19 and over They did not find within the groups any significant age or sex difference in the total, differential or absolute leukocyte counts or in the sedimentation rates The group differences in regard to the white blood cells are given in detail In regard to the sedimentation rate, the findings were generally the same for each group The greatest number of determinations fell in the lower ranges, and a rate of 15 mm in forty-five minutes represented the upper limit of normal values, it included 80 per cent of the results Higher values, they believe, were due to chronic infection in the tonsils, teeth or sinuses not detectable in the routine physical examination

Schultz and Rose²⁰ studied the "formol gel" reaction in the blood of patients with rheumatic fever, and their results suggest that this test may be a valuable aid in the diagnosis of active rheumatic carditis The test consists in adding 2 drops of a 40 per cent solution of formaldehyde to 1 cc of the serum to be tested With normal serum no obvious change occurs, but with pathologic serum an opaque gel forms This gel formation is invariably associated with hyperglobulinemia, although other factors may be important It is interesting that the increased sedimentation rate of red blood cells has a similar association Schultz and Rose found that in various febrile illnesses of nonrheumatic origin there was a parallelism between the "formal gel" test and the sedimentation rate but that in children as in adults with rheumatic carditis the results were unique Early in the course of rheumatic fever negative "formol gel" reactions are frequently associated with very rapid sedimentation rates With the development of active carditis, positive "formol gel" reactions may appear when the sedimentation rate has actually decreased, and during convalescence the sedimentation rate may drop to very low levels while the "formol gel" reaction remains strongly

19 Osgood, E E , Baker, R L , Brownlee, I E , Osgood, M W , Ellis, D M , and Cohen, W Total Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Adolescents Fifteen to Eighteen Years of Age, *J Lab & Clin Med* **24** 905, 1939, Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Children Four to Seven Years of Age, *Am J Dis Child* **58** 61 (July) 1939, Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children Standards for Children Eight to Fourteen Years of Age, *ibid* **58** 282 (Aug) 1939 Osgood, E E , Brownlee, I E , Osgood, M W , Ellis, D M , and Cohen, W Total Differential and Absolute Leukocyte Counts and Sedimentation Rates Determined for Healthy Persons Nineteen Years of Age and Over, *Arch Int Med* **64** 105 (July) 1939

20 Schultz, M P , and Rose, E J The Formol-Gel Reaction in Rheumatic Fever An Aid in the Diagnosis of Active Carditis, *Pub Health Rep* **54** 248, 1939

positive. In other words, the latter test is apparently more specific for active rheumatic carditis.

Clinical Features—Although the main clinical features of rheumatic heart disease have been known for a long time, many details still await clarification. The natural evolution of a disease with such widespread and diverse manifestations as rheumatic fever can be fully understood only as a result of studying large numbers of patients throughout their lifetime. This will require the work of many investigators over a long period. Additions to the knowledge of the clinical course of rheumatic fever are being made continually, and some day understanding of this disease will be complete. Last year a number of papers²¹ appeared dealing with widely varied aspects.

Ritchie, in the St. Cyres Lecture for 1939, brought the discussion of acute rheumatic carditis up to date. He stresses the great individual variations in the response to rheumatic fever and makes the interesting statement that even though the valves remain intact the myocardial lesions may lead to hypertrophy and dilatation of the heart. Jones and Mote have confirmed earlier experience that a close relationship exists between acute infections of the upper respiratory tract and initial or recurrent attacks of rheumatic fever. Bland and Jones find that about 30 per cent of young patients are left without demonstrable damage to the heart after their initial attack of rheumatic fever. In a ten year follow-up study of 314 such patients they found that signs of permanent valvular deformity developed in 25 per cent later on. This delayed appearance of heart disease was associated with recurrent rheumatic fever in two thirds of the group, while in the remaining third it developed insidiously. Massie and Levine studied the prognosis and subsequent developments in acute rheumatic pericarditis. They found that

21 Ritchie, W. T. Acute Rheumatic Carditis, *Lancet* **2** 582, 1939. Jones, T. D., and Mote, J. R. The Clinical Importance of Infection of the Respiratory Tract in Rheumatic Fever, *J. A. M. A.* **113** 898 (Sept 2) 1939. Altschule, M. D. The Relation Between Prolonged P-R Interval and Auricular Fibrillation in Patients with Rheumatic Heart Disease, *Am. Heart J.* **18** 1, 1939. Gauld, R. L., Ciocco, A., and Read, F. E. M. Further Observations on the Occurrence of Rheumatic Manifestations in the Families of Rheumatic Patients, *J. Clin. Investigation* **18** 213, 1939. Bruetsch, W. L. Chronic Rheumatic Brain Disease as a Cause of Mental Disorders, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **166** 4, 1939. Juster, I. R. The Significance of Rheumatic Activity in Chronic Rheumatic Heart Disease. II. A Method of Classification, *Am. Heart J.* **17** 669, 1939. Aschoff, L. Visceral Rheumatism During Childhood, *Arch. f. Kinderh.* **116** 145, 1939. Bacal, H. L., and Struthers, R. R. Rheumatic Infection in Childhood. Effect of Surgical Operations on Blood Sedimentation Rate, *Canad. M. A. J.* **40** 140, 1939. Bland, E. F., and Jones, T. D. Delayed Appearance of Heart Disease After Rheumatic Fever, *J. A. M. A.* **113** 1380 (Oct 7) 1939. Massie, E., and Levine, S. A. The Prognosis and Subsequent Developments in Acute Rheumatic Pericarditis, *ibid.* **112** 1219 (April 1) 1939.

although pericarditis is often associated with severe rheumatic infection yet, if the valves are spared, recovery is essentially complete, and the prognosis is good

Treatment—We have previously reviewed the results of investigators who have tested the therapeutic value of sulfanilamide in rheumatic fever. It was shown that the drug not only is of no value but actually aggravates the disease. Coburn and Moore²² have demonstrated further that sulfanilamide when administered to rheumatic subjects after the onset of streptococcal infection of the throat does not prevent rheumatic recrudescences. However, these investigators, as well as Thomas and France,^{23a} have found that daily administration of small amounts of sulfanilamide (1 to 3 Gm) provides almost certain protection against infection by the hemolytic streptococcus and rheumatic activity. Coburn, in a personal communication, urges caution in the use of sulfanilamide, the study still being in the experimental stage.

There have been further reports on the beneficial effect of fever therapy in chorea and in acute rheumatic fever.^{23b c d} It must be remembered nevertheless that this procedure is still new and that more work needs to be done before it can be generally recommended.

BACTERIAL ENDOCARDITIS

Streptococcus Viridans Endocarditis—Two excellent reviews appeared in 1939 on endocarditis due to *Streptococcus viridans*. Middleton and Burke²⁴ analyzed 88 cases observed at the Wisconsin General Hospital. On the whole, their findings are in accord with present day views regarding this disease. Contrary to the usual teaching, they state that congestive heart failure may sometimes attend or mask this condition. Therapy was uniformly unavailing and included such means as sodium cacodylate, immunotransfusions and the roentgen ray. There was one instance of healed endocarditis.

22 Coburn, A. F., and Moore, L. V. The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, with Especial Reference to Rheumatic Fever, *J. Clin. Investigation* **18** 147, 1939.

23 (a) Thomas, C. B., and France, R. Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *Bull. Johns Hopkins Hosp.* **64**:67, 1939. (b) Bauer, E. L. Further Studies on the Treatment of Chorea and Rheumatic Infection by Fever Induction, *Am. J. M. Sc.* **198** 224, 1939. (c) Simmons, E. E., and Dunn, F. L. Fever Therapy in Acute Rheumatic Disease, *Arch. Phys. Therapy* **20** 547, 1939. (d) Ishmael, W. K. The Use of Autohemotherapy Reinforced with Artificial Fever in Treatment of Rheumatic Disease, *J. Oklahoma M. A.* **32** 337, 1939.

24 Middleton, W. S., and Burke, M. *Streptococcus Viridans Endocarditis Lenta. A Clinico-Pathologic Analysis of the Experience in the Wisconsin General Hospital*, *Am. J. M. Sc.* **198** 301, 1939.

An article by Capps²⁵ has been received with unusual interest because of his earlier report of cures following the use of sodium cacodylate. He has studied 139 patients, all followed to the time of death or over a long period of years up to 1937 or 1938. Of the 139 patients, 11 were living from eight to twenty-six years after the attack of endocarditis. These patients with 1 exception were not very ill, and none was suspected of having endocarditis until the appearance of heart murmurs, embolic signs, enlargement of the spleen and positive blood cultures. Curiously enough, all 11 patients were seen prior to 1925, and 7 of the 11, in the years 1923 and 1924, corresponding to the peak incidence of all cases. Capps speculates as to the possibility that the large number of cases observed in the early twenties represented an epidemic in which a milder type of infection was encountered. Or, again, that *Str. viridans* may go through cycles of changing virulence. He is of the opinion that sodium cacodylate therapy played a minor role and that it is patients with a mild degree of infection who recover.

Recent studies have provided fresh hope for success in the treatment of bacterial endocarditis. This notable achievement has been made possible through the remarkable curative properties of sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and the action of heparin in preventing thrombus formation. In bacterial endocarditis the organisms are protected from the natural immune bodies by the accumulating platelet thrombi and debris which form the vegetations on the cardiac valves. The introduction of highly purified heparin, which may be given intravenously, has made it possible to prevent the formation of platelet thrombi in dogs and, it is reasonable to assume, to prevent additional accumulation of platelets in vegetations already formed. This would allow greater opportunity for the chemotherapeutic agents to come into contact with the invading organism. There is another important factor and that is the degree of natural immunity of the host. It has long been believed that the blood of patients with bacterial endocarditis has a high specific antibody titer. Recent observations²⁶ have shown, however, that this is far from true and that the antibody titer is frequently very low.

Kelson and White²⁷ report their experience with 7 patients who were treated for *Str. viridans* endocarditis with sulfapyridine and heparin. From 4 to 6 Gm of sulfapyridine was given daily before and

25 Capps, J. A. Subacute Bacterial Endocarditis Due to *Streptococcus Viridans* with Special Reference to Prognosis, *Ann Int Med* **13** 280, 1939.

26 Orgain, E. S. Personal communication to the author.

27 Kelson, S. R., and White, P. D. A New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination. Preliminary Report, *J. A. M. A.* **113** 1700 (Nov. 4) 1939.

during the use of heparin and for one week afterward Heparin (10,000 units in 500 cc of saline solution) was administered by continuous intravenous drip (15 to 25 drops a minute) over a period of two weeks Two patients had reactions to the heparin, and treatment was discontinued, and 2 patients died within a few days The remaining 3, who were able to take heparin for more than one week, showed striking improvement and were free of all evidence of the disease nineteen, eighteen and four weeks, respectively, after treatment was discontinued One of these 3, a young man, died of active rheumatic endocarditis several months after treatment for subacute bacterial endocarditis, and at autopsy the lesions of the bacterial endocarditis were found to be healed The authors stress the fact that this procedure is still in the experimental stage and that it is not to be recommended except under close and careful observation Recent communications from these workers indicate a high percentage of failures in the further trial of this treatment but with a few patients observed in whom the condition has apparently been controlled by continued administration of sulfapyridine or sulfathiazole (2-[paraaminobenzene]-thiazole) To date it is too early to recognize cures in the patients except in 1, of the first series, who is now perfectly well a year after treatment One of the patients in the first series who appeared to have been treated successfully suffered a relapse two months after stopping treatment, but his condition is again under control after a second course There is some question as to the practical value of heparin, certainly the chemotherapy is apparently the most important part of the treatment There is evidently a great difference in the reaction of different strains of *Str viridans* to the drugs, and much further study of this aspect is necessary

Friedman, Hamburger and Katz²⁸ report their observations on a patient with subacute bacterial endocarditis who was treated with heparin and who died during treatment as a result of cerebral hemorrhage Despite the fact that emboli had been given off repeatedly, the cardiac valves, at autopsy, showed only small "clean" vegetations, and there were two necrotic areas on the vegetations, possibly indicating the dissolution of some of the fibrin

Spink and Crago²⁹ administered sulfanilamide to 11 patients with *Str viridans* endocarditis and to 1 patient with *Staphylococcus albus* endocarditis The last-mentioned patient was apparently cured but died following a relapse seven months later Only 1 of the others 10 was

28 Friedman, M., Hamburger, W. W., and Katz, L. N. Use of Heparin in Subacute Bacterial Endocarditis. A Preliminary Report, *J. A. M. A.* **113** 1702 (Nov. 4) 1939

29 Spink, W. W., and Crago, F. H. Evaluation of Sulfanilamide in the Treatment of Patients with Subacute Bacterial Endocarditis, *Arch. Int. Med.* **64** 228 (Aug.) 1939

definitely improved, and she has remained in good health for nine months. Spink and Crago believe that sulfanilamide and its related compounds will be of doubtful value in the treatment of patients with subacute bacterial endocarditis because of the nature of the focus of infection, the proliferating mass of bacteria beneath the vegetations being too well protected from the action of drugs and antibodies.

Solway and Pritzker³⁰ report their observations on a patient with endocarditis due to *Streptococcus haemolyticus*. Spectacular improvement followed the administration of sulfanilamide, but after an interval of five months relapse and death followed.

Gonococcic Endocarditis—Organ and Poston³¹ describe a case of bacterial endocarditis due to the gonococcus and a nonhemolytic anaerobic streptococcus superimposed on the pulmonary valve. Recovery followed the oral administration of sulfapyridine in moderate-sized doses. Of the two organisms, the gonococcus proved the more vulnerable to chemotherapy, since it disappeared from the blood first. Coincident with the disappearance of the bacteremia, immune bodies appeared, and in a high titer, and the complement fixation test for the gonococcus, initially 4 plus, became negative. The authors believe that these immunologic changes, together with the clinical improvement, are probably indicative of cure.

Fletcher and Scott³² report their experience with sulfanilamide in the treatment of gonococcic endocarditis. Three of the 4 patients treated died, the fourth recovered. The authors point out that although the condition of the patient who recovered from her illness did not completely fulfil the most rigid criteria for establishing the diagnosis, the presence of gonococcic endocarditis seemed very likely.

ARTERIAL HYPERTENSION

Standardization of Blood Pressure Readings—Sir Thomas Lewis, in his book, "Diseases of the Heart", states that "the fingers should be trained to recognize a high-tension pulse, for a pressure meter can hardly be used as a routine in general practice." This statement has provoked much criticism, for many observers are of the opinion that this method is grossly inaccurate and that every physician should own and

30 Solway, L. J., and Pritzker, H. G. Sulphanilamide in the Treatment of Bacterial Endocarditis, *Canad. M. A. J.* **40**: 543, 1939.

31 Organ, E. S., and Poston, M. A. Gonococcal Endocarditis with Recovery After Sulfapyridine. Report of a Case, *New England J. Med.* **221**: 167, 1939.

32 Fletcher, P. H., and Scott, V. C. Four Cases of Gonococcic Endocarditis Treated with Sulfanilamide, with Recovery of One, *Bull. Johns Hopkins Hosp.* **65**: 377, 1939.

use a sphygmomanometer. The recommendations recently proposed³³ for taking and recording blood pressure certainly represent a point of view different from that of Lewis. While these recommendations are excellent in themselves, it is likely that the general physician will find certain details impracticable. Nevertheless, there is convincing evidence, which will be presented later, that in certain ranges of blood pressure great accuracy is desirable. The chief recommendations are given here-with in abbreviated form.

1 **Blood Pressure Equipment** The equipment to be used, whether mercurial or aneroid, should be in good condition and calibrated at yearly intervals for accuracy, and more often if defects are suspected.

2 **The Patient** The patient should be comfortably seated, with the arms slightly flexed and the whole forearm supported at the level of the heart on a smooth surface.

3 **Position and Method of Application of the Cuff** A standard-sized cuff containing a rubber bag from 12 to 13 cm. in width should be used. A completely deflated cuff should be applied snugly and evenly around the arm with the lower edge about 1 inch (2.5 cm.) above the antecubital space and with the rubber bag applied over the inner aspect of the arm.

4 **Significance of Palpatory and Auscultatory Levels** In all cases palpation should be used as a check on auscultatory readings.

5 **Position and Method of Application of the Stethoscope** The stethoscope should be placed over the previously palpated brachial artery in the antecubital space, not in contact with the cuff.

6 **Determination of the Systolic Pressure** The cuff should be rapidly inflated to a pressure about 30 mm. above the level at which the radial pulse can be palpated. The cuff should then be deflated at a rate of from 2 to 3 mm. of mercury per second. The level at which the first sound regularly appears should be considered the systolic pressure unless, as already stated, the palpatory level is higher, in which event the palpatory level should be accepted. This should be noted.

7 **Determination of the Diastolic Pressure and the Pulse Pressure** With continued deflation of the cuff, the point at which the sounds suddenly become dull and muffled should be known as the diastolic pressure. If there is a difference between that point and the level at which the sounds completely disappear, the American committee recommends that the latter reading should be regarded also as the diastolic pressure. This should then be recorded in the following form: RT (or LT)

³³ Standard Method for Taking and Recording Blood Pressure Readings by the Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the Committee for the Standardization of Blood Pressure Readings of the Cardiac Society of Great Britain and Ireland, J. A. M. A. **113**:294 (July 22) 1939.

140/80-70 or 140/70-0 If these two levels are identical, the blood pressure should be recorded as follows 140/70-70 The cuff should be completely deflated prior to any further determinations

In our opinion the first two sentences under the last heading do not logically follow each other, that is to say, if the sounds become dull and muffled, they cannot, at the same point, disappear completely Furthermore, there is little evidence to support the view that the level at which there is complete disappearance of all sounds should also be regarded as the diastolic pressure, but it may be well to note this level

The committee's explanatory comments and further recommendations are valuable The necessity of knowing the physical and mental state of the patient at the time the blood pressure is recorded is worthy of emphasis A corollary of this is the suggestion that when especially careful studies of the blood pressure are to be made, the use of basal blood pressure conditions should be considered Helpful hints are given in regard to the determination of blood pressure in the presence of cardiac arrhythmias It should be recognized that the mercury sphygmomanometer, which has often been declared the more accurate instrument for recording blood pressure, may be in error Too rapid inflation or deflation of the cuff may result in a lag in the rise or fall of the mercury column, with an error even to 20 to 30 mm of mercury either systolic or diastolic if the stopper at the top of the mercury tube is too tight

Normal Blood Pressure—Most physicians are vague in their idea of what constitutes normal arterial blood pressure This is due in part to the fact that there are physiologic variations in the normal level of blood pressure and in part to the divergent opinions expressed by cardiologists, but, above all, to the fact that a truly comprehensive study of the normal blood pressure range has never been made The important contribution of Robinson and Brucer³⁴ has done much to clarify this problem, and their results, startling as they are, must be accepted until disproved

The report of Robinson and Brucer is based on a statistical study of (1) the blood pressure in 10,883 persons, (2) a study of five to ten year continuous blood pressure records of 500 persons and (3) an appraisal of mortality at various pressure levels

For the statistical study, 7,478 men and 3,405 women were selected, representing fairly typical portions of all age groups between 20 and 70 years under conditions of general health comparable to those of any

34 Robinson, S. C., and Brucer, M. Range of Normal Blood Pressure. A Statistical and Clinical Study of 11,383 Persons, *Arch Int Med* 64 409 (Sept) 1939

random group in the total population. For the men, the mean systolic blood pressure was found to be 121 mm of mercury (standard deviation of the mean, 17) and the diastolic pressure 74.4 (standard deviation, 10.5). For the women, the mean systolic pressure was 117 mm of mercury (standard deviation, 10.8) and the diastolic pressure 71 (standard deviation, 11.5). The authors point out that if one works only with a broad unselected sample it is better to determine where the values congregate than to use averages. Thus the modal blood pressure was 115 mm systolic and 71 mm diastolic for the men and 113 mm systolic and 70 mm diastolic for the women.

Since the whole group contained both normal and hypertensive persons, Robinson and Bruce rightly concluded that it was not justifiable to draw conclusions concerning normal levels of blood pressure from such a sample. Consequently they arbitrarily excluded all persons with a blood pressure of 140 mm systolic and 90 mm or over diastolic, this left a group including 13.3 per cent of the men and 11.5 per cent of the women. Study of this delimited group indicated that men usually have a blood pressure (modal) of 115 mm systolic and 72 diastolic and women a modal blood pressure of 112 mm systolic and 70 mm diastolic.

The next step was the analysis of a group of 500 records continuous over a period of five to ten years. This took into account the variations of blood pressure, which, for the most part, are due to the normal diurnal flux of pressure. They noted that the lower pressures did not show great variation (usually less than 10 mm) whereas the higher pressures usually varied by 15 to 40 mm. Furthermore, the low pressures (below 120 mm) almost invariably tended to remain at the same general low level throughout all age groups, while the higher pressures (120 mm or above) tended to rise to even higher levels with advancing years. Also, it was noted that once a person's pressure shows even intermittent rises into the danger zones of 120 to 130 and 130 to 140 mm, it frequently returns to that level. From these continuous records it was concluded that normal blood pressure should not exceed 120 mm.

The third analysis was made from a consideration of mortality data. The fundamental premise was made that "normal" blood pressure should be consistent with the longest possible life. In other words, what is the vascular tension that leads to the longest life span and what are the levels that shorten life? It was found that mortality increases in direct proportion to increased blood pressure. The important thing is that this holds true not only for the higher pressures (140 mm and higher) but also for pressures of 120 to 130 mm. There is even some evidence that a pressure of 110 systolic and 70 diastolic is associated with a lower mortality than one of 120 systolic and 80 diastolic.

The general conclusion is drawn that normal blood pressure for men and women is from 90 to 120 mm of mercury systolic and 60 to 80 mm diastolic. A normal person attains his mature blood pressure at about adolescence and keeps that range throughout life except for a slight rise at about the twentieth year. Transient elevations of blood pressure should not be ignored, as they often indicate beginning hypertension. Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive.

Essential Hypertension—The problem of essential hypertension is still unsolved. Recent studies have not yet revealed the nature of the responsible agent, although progress can be reported. It is by no means an easy matter to evaluate the mass of experimental and clinical data now available. So much work is actively going on along these lines that a review, which is limited to published data, is behind the times.

For a clear statement of the problem the reader is referred to Pickering's article,³⁵ in which he develops a line of thought rather than an attempt to prove a scientific hypothesis. The subject matter of his review has been previously discussed and need not be considered here.

Causes—There have been described a number of new methods for the production of permanent hypertension. Page,³⁷ during the course of experiments designed for another purpose, observed that hypertension developed in animals in which cellophane had been wrapped around the kidneys. Cellophane causes perinephritis, which results in the formation of a fibrocollagenous hull that constricts the renal parenchyma. Similarly, Greenwood, Nassim and Taylor³⁸ produced permanent hypertension in dogs by applying a collodion cast to one kidney and removing the other. They raise the question as to whether or not the prevention of renal hypertrophy is the provocative factor. It seems that in both sets of experiments the mechanism responsible for the hypertension is similar to that which results from constricting the renal artery by means of the Goldblatt clamp.

Drury,³⁹ in an excellent study which we failed to review last year, described a unique method for the production of hypertension in rab-

35 Pickering, G. W. The Problem of High Blood Pressure in Man, *Brit M J* **1** 1, 1939.

36 Footnote deleted by the author.

37 Page, I. H. The Production of Persistent Arterial Hypertension by Cellophane Perinephritis, *J A M A* **113** 2046 (Dec 2) 1939, A Method for Producing Persistent Hypertension by Cellophane, *Science* **89** 273, 1939.

38 Greenwood, W. F., Nassim, R., and Taylor, N. B. The Production of Hypertension by the Prevention of Kidney Hypertrophy, *Canad M A J* **41** 443, 1939.

39 Drury, D. R. The Production by a New Method of Renal Insufficiency and Hypertension in the Rabbit, *J Exper Med* **68** 693, 1938.

bits The method consists in placing a ligature loosely around the left renal artery of a baby rabbit and allowing the artery to grow up to the size of the loop The development of the left kidney is arrested at this stage and remains dwarfed, while the right hypertrophies Hypertension occurs even in the presence of the hypertrophied right kidney when there is good renal function After removal of the right kidney the hypertension is increased Here, again, the underlying mechanism of the production of hypertension is probably the same as in the Goldblatt experiment, but Drury's method offers many advantages

Goldblatt, Kahn and Hanzal⁴⁰ confirmed the work of Rytand in showing that constriction of the aorta just above the level of the renal arteries is followed by hypertension, while constriction just below the level of the renal arteries has no significant effect on the blood pressure above that level

A number of papers have been published⁴¹ on the nature and action of the renal pressor substance It is probable that this substance is renin, and it has now been prepared in a highly purified form, a minute amount being sufficient to elevate the blood pressure considerably Repeated injections result in a diminution of the pressor response, and this is due, according to Page, to loss of "renin-activator" and the development of an "ant substance"

Clinical Studies—Weiss and Parker,⁴² in a fundamental study on pyelonephritis, showed that this disease in the chronic and in the healed stage should be considered as one type of Bright's disease, for it can lead to kidney failure, severe hypertension and their complications They studied the natural history of the disease in 100 selected cases and were able to trace the sequence of events from the initial renal lesions to the terminal stage of severe hypertension They found that hypertension is frequently associated with pyelonephritis and that this association is responsible for 15 to 20 per cent of all cases of malignant

40 Goldblatt, H, Kahn, J R, and Hanzal, R F Studies on Experimental Hypertension IX The Effect on Blood Pressure of Constriction of the Abdominal Aorta Above and Below the Site of Origin of Both Main Renal Arteries, J Exper Med **69** 649, 1939

41 Page, I H On the Nature of the Pressor Action of Renin, J Exper Med **70** 521, 1939 Helmer, O, and Page, I H Purification and Some Properties of Renin, J Biol Chem **127** 757, 1939 Williams, J R, Diaz, J T, Burch, J C, and Harrison, T R The Relation of the Adrenal Glands to the Action of the Renal Pressor Substance, Am J M Sc **198** 212, 1939 Swingle, W W, Taylor, A R, Collings, W D, and Hays, H W Preparation and Bioassay of Renin, Am J Physiol **127** 768, 1939 Prinzmetal, M, Friedman, B, and Abramson, D I The Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, Ann Int Med **12** 1604, 1939

42 Weiss, S, and Parker, F, Jr Pyelonephritis Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18** 221, 1939

hypertension In hypertension accompanying pyelonephritis the symptoms are commonly those of uremia rather than those of severe coronary or cerebral arteriosclerosis, cerebral encephalopathy, neuroretinitis and high cerebrospinal fluid pressure as well as the syndrome of left ventricular failure were frequently observed It is emphasized that pyelonephritis is the one renal disease which in its incipient stage can be treated effectively

Among a number of important papers⁴³ relating to various clinical aspects of hypertension, the monograph by Wagener and Keith on diffuse arteriolar disease with hypertension and the associated retinal lesions is especially noteworthy They found it possible, from the standpoint of prognosis at least, to divide all cases of essential hypertension into four groups In the first two the hypertension is relatively benign and the lesion in the retinal arterioles is essentially anatomic resulting either from previous angiospastic episodes or from long-continued increase in arteriolar tonus without active angiospastic episodes In the last two groups the hypertension is severe or "malignant," and the essential lesion in the arterioles is active spastic constriction superimposed either on increased arteriolar tonus or on anatomic thickening of the walls of the arterioles or on both

Hypertension in Eclampsia—The newer studies on experimental hypertension have offered a plausible explanation for the "toxemias" of pregnancy, the most constant sign of which is arterial hypertension There is considerable evidence⁴⁴ that a humoral factor is involved

43 Wagener, H P, and Keith, N M Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, *Medicine* **18** 317, 1939 Friedman, B, and Prinzmetal, M Vasomotor Effects of Blood in Patients with Hypertension and Animals with Experimental Hypertension, *Ann Int Med* **12** 1617, 1939 Schroeder, H A, and Steele, J M Studies on "Essential" Hypertension I Classification, *Arch Int Med* **64** 927 (Nov) 1939 Williams, J R, Jr, and Harrison, T R Clinical Pictures Associated with Increased Blood Pressure Study of One Hundred Patients, *Ann Int Med* **13** 650, 1939 Keith, N M, Wagener, H P, and Barker, N W Some Different Types of Essential Hypertension Their Course and Prognosis, *Am J M Sc* **197** 332, 1939 de Wesselow, O L V S, and Thomson, W A R Study of Some Serum Electrolytes in Hypertension, *Quart J Med* **8** 361, 1939 Rasmussen, H, and Thingstad, R Cardiovascular Changes in Essential Hypertension, with Special Reference to Electrocardiogram in Hypertension, *Acta med Scandinav* **101** 237, 1939 Page, I H A Clinical Study of Malignant Hypertension, *Ann Int Med* **12** 978, 1939 Wilson, C, and Byrom, F B Renal Changes in Malignant Hypertension, *Lancet* **1** 136, 1939 Mosenthal, H O, and Lander, H H The Development and Importance of Hypertension in Chronic Bright's Disease, *Ann Int Med* **12** 1449, 1939

44 Page, E W, and Ogden, E The Physiology of Hypertension in Eclampsia, *Am J Obst & Gynec* **38** 230, 1939 Dieckmann, W J, and Brown, I Do

just as in the hypertension due to renal ischemia. One theory is that chorionic tissue is responsible for this pressor factor and that the stimulus for the production of the latter may be an inadequate supply of blood to the placenta. Another possible explanation, which has some basis in experimental fact, is that pregnancy increases susceptibility to renal ischemia, which in turn may give rise to hypertension.

Treatment—One of the most dramatic medical announcements that could be made would be that a "cure" has been found for hypertension. More than a hint of this is to be found in the news letter of a recent issue of *Science*. However, the authors themselves⁴⁵ are uncertain as to the ultimate value of their method of treatment. And, whereas they can lower the blood pressure of hypertensive animals by oral administration of a kidney extract which does not lower the blood pressure of normal animals, they are uncertain as yet whether such a lowering is desirable or not. Furthermore, they found that in certain instances the animals became quite ill after their blood pressure had fallen and that some of the animals died. Because of this and because the extract is extremely difficult and expensive to prepare in adequate amounts for human use, the clinical experience has been most limited. One or two patients have shown practically no change in blood pressure, possibly owing to inadequate dosage. Several patients have shown what has appeared to be a rather encouraging drop of 20 to 40 mm of mercury and some simultaneous improvement in their symptoms. Even though these patients were carefully controlled, having been in the hospital for several weeks or longer in most instances, there is still a possibility that the declines observed in them may have been due to a psychic effect or may have been spontaneous. The results in patients may be regarded as encouraging but as not by any means convincing at the present time.

There have been two brief reports⁴⁶ on attempted revascularization of the kidney in an effort to lower the blood pressure in patients with hypertension. The theoretic basis for this procedure rests in the fact

Eclampsia and Preeclampsia Cause Permanent Vascular Renal Pathology? *ibid* **37** 762, 1939. Browne, F. J., and Dodds, G. H. The Remote Prognosis of the Toxemias of Pregnancy, *J Obst & Gynaec Brit Emp* **46** 443, 1939. Dill, L. V., Isenhour, C. E., and Cadden, J. F. The Effect of Quantitative Reduction of Renal Blood Flow upon the Pregnant Rabbit, *J Clin Investigation* **18** 641, 1939.

45 Harrison, T. R. Personal communication to the author.

46 Bruger, M., and Carter, R. F. Evidence of Communication Between Renal and Omental Blood Vessels Following Nephroomentopexy for Arterial Hypertension in Man. Preliminary Note, *Am J M Sc* **197**:832, 1939. Abram, P., Iselin, M., and Wallich, R. Attempt to Treat Arterial Hypertension of Renal Origin by Surgical Vascularization of the Kidney (Nephro-Omentopexy), *Presse méd* **47** 137, 1939.

that hypertension produced experimentally by compression of the renal artery may be relieved following the development of collateral circulation. The procedure consists in enveloping the kidney with omentum (nephro-omentopexy). It has been shown by O'Shaughnessy and others that cardio-omentopexy may aid in reestablishing the coronary circulation, and there is every reason to believe that an anastomotic circulation will develop between the kidney and the omentum. However, the two situations are not comparable, and in the case of the kidney it is doubtful if much good can be accomplished.

Except for nephro-omentopexy, there has not been any new development in the surgical treatment of hypertension.⁴⁷ Nowak and Walker,⁴⁸ largely on theoretic grounds, criticize this form of treatment, and Volini and Flaxman,⁴⁹ observing the symptomatic relief and the reduction in blood pressure resulting from nonspecific surgical measures, hold that the relief is comparable to that following resection of the splanchnic nerve.

Observations by Wood and Cash⁵⁰ and Short and Johnson⁵¹ confirm previous impressions that blood pressure increases with increase in body weight.

CORONARY HEART DISEASE

Coronary Occlusion and Cardiac Infarction—In continuation of the excellent series of articles on heparin, Solandt, Nassim and Best⁵² describe experiments in which the formation of cardiac mural thrombi in dogs was prevented by injecting heparin intravenously. Their method of regularly producing mural thrombi is of interest. In previous studies

47 Pahard, F., and Etienne-Martin, P. Surgical Treatment of Malignant Arterial Hypertension. Results and Indications, *Presse med* **47** 893, 1939. Smithwick, R. H. Surgery of the Sympathetic Nervous System, *New England J Med* **220** 475, 1939. Chabanier, H., Gaume, P., and Lobo-Onell, C. Survey Over Results of Interventions Practiced in Forty-Nine Cases of Nephro-Angioscleroses (Permanent Hypertensive States with Renal Lesions of Arterial Origin), *Presse méd* **46** 1818, 1938. Davis, L., and Barker, M. H. Clinical and Experimental Experiences in Surgical Treatment of Hypertension, *Ann Surg* **110** 961, 1939.

48 Nowak, S. J. G., and Walker, I. J. Experimental Studies Concerning the Nature of Hypertension. Their Bearing on Surgical Treatment, *New England J Med* **220** 269, 1939.

49 Volini, I. F., and Flaxman, N. The Effect of Nonspecific Operations on Essential Hypertension, *J A M A* **112** 2126 (May 27) 1939.

50 Wood, J. E., Jr., and Cash, J. R. Obesity and Hypertension. Clinical and Experimental Observations, *Ann Int Med* **13** 81, 1939.

51 Short, J. J., and Johnson, H. J. An Evaluation of the Influence of Overweight on Blood Pressures of Healthy Men. A Study of 3,516 Individuals Applying for Periodic Health Examination, *Am J M Sc* **198** 220, 1939.

52 Solandt, D. Y., Nassim, R., and Best, C. H. Production and Prevention of Cardiac Mural Thrombosis in Dogs, *Lancet* **2** 592, 1939.

on coronary occlusion it was found that simply tying the coronary vessels supplying the tip of the left ventricle did not result in the formation of a thrombus in over 100 animals. However, if sodium ricinoleate was injected into the heart muscle just beneath the endocardium, large pendulous thrombi were usually found within half an hour. In a series of animals on which the autopsies were performed one and one-half hours after the injection of the sclerosing solution, macroscopic cardiac mural thrombi were present in every animal, whereas, in comparable experiments, when heparin was administered no macroscopic thrombi were seen, although microscopic clumps of platelets were present in many of the animals. The same results were obtained in two series of animals on which autopsies were performed twenty-four hours after the hearts had received injections except that in the animals receiving heparin neither macroscopic nor microscopic thrombi were found. The authors pointed out that it is probable that after clinical coronary thrombosis several days must elapse before necrosis becomes sufficiently severe to induce the formation of mural thrombi and that thrombi might be prevented, therefore, even if the administration of heparin was started some considerable time after the initial thrombosis. Just how long the administration of heparin must be continued to permit a degree of healing such that thrombosis is no longer likely to occur must be decided by clinical trial. We agree that a clinical trial is justified, but certain complications and hazards must be kept in mind. In man the development of cardiac infarction is sometimes a gradual or intermittent process, and the onset of symptoms need not necessarily herald the onset of infarction. Thus, it is possible that mural thrombi may already be present at the time of onset of severe symptoms, before the indication for heparin is clear. Moreover, since fresh mural thrombi are sometimes laid down weeks to months after the acute infarction has occurred, the administration of heparin, to be certainly effective, might have to be continued for a very long period of time. And, incidentally, one may well hesitate to add the strain and potential danger of heparin therapy even for a short time to the condition of a patient very ill with acute coronary thrombosis.

Manning, McEachern and Hall⁵³ describe some interesting observations following sudden occlusion of coronary arteries in dogs. When the anterior descending branch of the left coronary artery was occluded, the mortality was less than 10 per cent for anesthetized dogs and about 40 per cent for conscious ones. The mortality following sudden occlusion of the left circumflex branch was found to be 25 per cent with anesthesia and about 75 per cent without. Satisfactory proof of the cause of the

53 Manning, G. W., McEachern, C. G., and Hall, G. E. Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches. *Arch Int Med* 64:661 (Oct) 1939.

greater mortality in the conscious animals is not given. There is evidence that it is not the result of changes in the systemic blood pressure, but the authors believe there may be a reflex spasm of collateral arterioles and small arteries producing additional areas of ischemia.

Controversy⁵⁴ continues to rage over the question of the possible precipitating factors in occlusion of a coronary artery. This question is of the first importance from both the scientific and the practical point of view, and fruitful discussion should be welcomed. The whole problem bristles with difficulties and is not likely to be resolved at once. It is highly doubtful if purely clinical studies will provide more than a partial answer, and they may even be misleading. This is so, in part at least, because of the uncertain time relation between the beginning of coronary occlusion and myocardial infarction. One cannot help being impressed with the fact that many persons with marked coronary atherosclerosis never suffer acute coronary occlusion and cardiac infarction. This being so, there must be precipitating factors of coronary occlusion, the occlusion cannot be regarded as a purely fortuitous event.

Two papers⁵⁵ have appeared on myocardial infarction not due to frank occlusion of a coronary artery. Undoubtedly this is a more common phenomenon than is ordinarily supposed, Friedberg and Horn noted it in 31 per cent of the last 1,000 autopsies performed in cases of myocardial infarction. It occurs most commonly in the presence of pulmonary embolism, calcific aortic stenosis and marked coronary narrowing.

Mallory, White and Salcedo-Salgar⁵⁶ made an important study on the speed of healing of myocardial infarcts, based on 72 autopsies. They describe the characteristic gross and microscopic features of infarcts of various ages and state that the age of an infarct can be judged fairly accurately during the first three weeks but not thereafter. The size and position of the infarct and the state of the remaining myocardial circulation are important determinants of the speed of healing. It was found that small infarcts heal in about five weeks and large

54 Master, A. M., Dack, S., and Jaffe, H. L. Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, *Arch Int Med* **64** 767 (Oct) 1939, Activities Associated with the Onset of Acute Coronary Artery Occlusion, *Am Heart J* **18** 434, 1939. Boas, E. P. Angina Pectoris and Cardiac Infarction from Trauma or Unusual Effort, with a Consideration of Certain Medicolegal Aspects, *J A M A* **112** 1887 (May 13) 1939.

55 Friedberg, C. K., and Horn, H. Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J A M A* **112** 1675 (April 29) 1939. Gross, H., and Sternberg, W. H. Myocardial Infarction Without Significant Lesions of Coronary Arteries, *Arch Int Med* **64** 249 (July) 1939.

56 Mallory, G. K., White, P. D., and Salcedo-Salgar, J. The Speed of Healing of Myocardial Infarction, *Am Heart J* **18** 647, 1939.

ones in about eight. Rupture of the heart is most common during the first week, may occur during the second but is rare thereafter. The subendocardial muscle layer often escapes, and another interesting finding is that the age of a mural thrombus is often much less than the age of the infarct itself, i. e., that mural thrombi may be laid down over old infarcts, especially if there is aneurysmal dilatation, weeks or months after the original dilatation.

Cardiac Aneurysm—Last year we mentioned briefly a paper by Parkinson, Bedford and Thomson⁵⁷ on cardiac aneurysm. Their report deserves fuller discussion in connection with the increased interest in the subject. They trace the evolution of our knowledge concerning this condition, pointing out that up to 1914 only 3 reported cases of cardiac aneurysm had been correctly diagnosed during life. From an analysis of published statistics it appears that cardiac aneurysm occurred in 9 per cent of cases of cardiac infarction examined at autopsy. In 13 of the authors' 16 cases the cardiac aneurysm was due to coronary occlusion, in 11 the left anterior descending branch was occluded. In the remaining 3 cases it was associated with rheumatic heart disease. Other relatively common causes are syphilitic, congenital or traumatic heart disease. The most common sites of ventricular aneurysm are the apex and the anterior wall of the left ventricle. Incidentally, it is the opinion of the reviewers that a slight degree of aneurysmal dilatation of the left ventricle in the region of the myocardial infarct from coronary thrombosis is a common finding, though large sacs are infrequent.

There are few characteristic symptoms or signs of ventricular aneurysm, the diagnosis being made usually with the aid of the roentgen ray. Typically, ventricular aneurysm appears a week or two after cardiac infarction, and there may be pain over the apex of the heart. There may be palpable a pulsation over the aneurysm separate and distinct from the apical pulsation. The heart sounds are often faintly heard or muffled, and it is of interest that the first case correctly diagnosed (Remlinger, 1896) exhibited a double murmur presumably due to blood passing in and out through the mouth of the aneurysmal sac.

Parkinson and his associates did not describe any distinctive electrocardiographic features of cardiac aneurysm but noted the common occurrence of tracings indicating cardiac infarction. Nordenfelt⁵⁸ and Eliaser and Königsberg⁵⁹ describe certain electrocardiographic charac-

57 Parkinson, J., Bedford, D. E., and Thomson, W. A. R. Cardiac Aneurysm, *Quart J Med* 7:455, 1938.

58 Nordenfelt, O. The Electrocardiogram in Chronic Aneurysm of the Heart, *Acta med Scandinav* 102:101, 1939.

59 Eliaser, M., Jr., and Königsberg, J. Electrocardiographic Findings in Cases of Ventricular Aneurysm, *Arch Int Med* 64:493 (Sept) 1939.

teristics which they believe to be presumptive evidence of ventricular aneurysm Nordenfelt advances the suggestion that often electrocardiograms taken of a patient with a large chronic aneurysm on the anterior wall of the ventricle will show relatively low R waves in lead I, prominent S waves in leads II and III, elevated ST segments in all leads, inversion of the T waves, in lead I, and upright T waves in leads II and III There may be prominent Q waves in lead I In lead IV the R waves are absent and the ST segments elevated Eliaser and Konigsberg found that in over a fourth of the cases of aneurysm of the left ventricle the electrocardiogram shows inversion of the chief initial ventricular deflection and the T waves in lead I with the P waves remaining upright In over a third of the cases the electrocardiogram shows inversion of the chief initial ventricular deflection in leads II and III and a corresponding upright deflection in lead I that may or may not be of low amplitude

Of chief importance in the diagnosis of cardiac aneurysm are the roentgenologic findings, which are summarized by Parkinson and his associates as follows

- 1 Enlargement of the left ventricle with deformity of its contour
- 2 A localized protuberance inseparable from the heart shadow on rotation of the patient
- 3 Abnormal or absent pulsation of the aneurysmal zone
- 4 Evidence of adhesions between the heart and the chest wall or diaphragm
- 5 Calcification of the wall of the sac or of its contained clot

We should like to refer also to the roentgeno-kymographic findings of absence of pulsation of, or paradoxical pulsation of, cardiac aneurysms as a diagnostic aid in myocardial infarction

Angina Pectoris—A number of papers⁶⁰ have been published on various clinical aspects of angina pectoris Of particular interest is the

60 (a) Muller, C Angina Pectoris in Hereditary Xanthomatosis, Arch Int Med **64** 675 (Oct) 1939 (b) Spillane, J D, and White, P D Herpes Zoster and Angina Pectoris, Brit Heart J **1** 291, 1939 (c) Gilbert, N C Vasomotor Changes in the Coronary Arteries and Their Possible Significance, J A M A **113** 1925 (Nov 25) 1939 (d) Katz, L N, and Lindner, E The Reaction of the Coronary Vessels to Drugs and Other Substances, *ibid* **113** 2116 (Dec 9) 1939 (e) Mainzer, F Persistent Pain Localized at a Distance From the Heart (Shoulder, Epigastric Region) in Coronary Insufficiency, Acta med Scandinav **101** 541, 1939 (f) Wahlberg, J Esophageal Spasm as Cardiac Symptom, *ibid* **101** 568, 1939 (g) Clerc, A, and Sterne, J 1262 F (Diethyl-Amino-Ethoxy-2-Diphenyl) in Treatment of Anginal Syndromes, Presse méd **47** 1517, 1939 (h) Brumm, H J, and Willius, F A The Surgical Risk in Patients with Coronary Disease, J A M A **112** 2378 (June 10) 1939 (i) White, P D The Immediate and Ultimate Prognosis in Heart Disease with Especial Reference to "Permanent Total Disability," *ibid* **112** 2380 (June 10) 1939 (j) Sprague, H B Mental Adjustments to Heart Disease The Factors Involved in Disability, *ibid* **112** 2384 (June 10) 1939

report of Muller on the relationship between angina pectoris and hereditary xanthomatosis. He studied 76 cases of xanthomatosis, in 68 there was associated heart disease, and a diagnosis of angina pectoris was made in 59. Muller points out that the syndrome of cutaneous xanthomatosis, hypercholesteremia and angina pectoris presents itself as a well defined clinical disease at an early age and that it may be transmitted as a dominant hereditary disease.

Spillane and White^{60b} describe 12 instances of the occurrence of herpes zoster in anginal subjects. In 10 of these the herpetic eruption appeared after the anginal attacks had become established, while in the remaining 2 it appeared about two years before the angina. In every instance there was a close relationship between the distribution of the eruption and that of the anginal pain. It is suggested that repeated bombardment of spinal root ganglions by afferent impulses from the ischemic heart gives rise to antidromic impulses that lead to the formation of blisters.

There has been continued interest in surgical procedures designed for the relief of angina pectoris.⁶¹ Raney^{61b} reports amazing success in the relief of pain by section of the ramus communicantes (2-5) from the intercostal nerves and section of the sympathetic chain between the fifth and sixth dorsal ganglions on the left side. Unfortunately, most of the report is concerned with rather unimpressive arguments attempting to justify the procedure on theoretic grounds. Except for 2 case reports, only meager clinical details are given. Eleven patients with "desperate attacks" of angina pectoris were all completely relieved of pain by means of the aforementioned operation.

SPONTANEOUS MEDIASTINAL EMPHYSEMA

This syndrome⁶² is mentioned here because of the importance of differentiating it from acute cardiac infarction. In fact, Hamman's^{62a} first case was so diagnosed at the time of onset of symptoms. This author has summarized the essential clinical features as follows:

1. Interstitial emphysema of the lung may occur without the least effort, when the patient is quietly standing, sitting or lying down.

61 (a) O'Shaughnessy, L., Slome, D., and Watson, F. Surgical Revascularization of the Heart. The Experimental Basis, *Lancet* **1** 617, 1939. (b) Raney, R. B. A Hitherto Undescribed Surgical Procedure Relieving Attacks of Angina Pectoris. Anatomic and Physiologic Basis, *J. A. M. A.* **113** 1619 (Oct. 28) 1939.

62 (a) Hamman, L. Spontaneous Mediastinal Emphysema, *Bull. Johns Hopkins Hosp.* **64** 1, 1939. (b) A Note on the Mechanism of Spontaneous Pneumothorax, *Ann. Int. Med.* **13** 923, 1939. (c) McGuire, J., and Bean, W. B. Spontaneous Interstitial Emphysema of the Lungs, *Am. J. M. Sc.* **197** 502, 1939.

2 When the air reaches the mediastinum, distending the mediastinal tissues the patient complains of pain which is often very severe. Usually the pain is located beneath the sternum, sometimes it radiates to the back, at other times to the neck and shoulders, rarely to the arms. Accompanying the pain there is often a sensation of pressure or of expansion beneath the sternum.

3 There are no constitutional symptoms, no evidence of shock. The temperature, the pulse and respiratory rates, the blood pressure, the leucocyte count are very little if any altered.

4 In many instances a peculiar and distinctive sound is heard over the heart synchronous with its contractions. Usually the sound is heard only during systole but at times it may be heard also during diastole.

5 The area of cardiac dulness is diminished or completely obliterated, the dulness being replaced by a hyperresonant percussion note.

6 Pneumothorax often occurs. The pneumothorax is usually small and may not be suspected until a roentgenogram of the chest has been taken.

7 The roentgenogram is a valuable aid in establishing the diagnosis. In instances in which the characteristic sound over the heart is absent the roentgenographic evidence of air in the mediastinum may be decisive.

8 When air appears in the subcutaneous tissues of the neck the diagnosis is at once assured.

GLYCOGEN DISEASE

Van Creveld⁶³ has written a comprehensive treatise on glycogen disease, which includes a section on cardiomegalia glycogenica. He points out the importance of this condition in explaining many cases of so-called congenital idiopathic hypertrophy of the heart. He states that glycogen disease should be suspected when, at examination, a child is found to have a large heart without valvular lesions or an anomaly of development of which the enlargement may be the consequence.

HEART DISEASE RESULTING FROM DEFORMITIES OF THE CHEST

Chapman, Dill and Graybiel⁶⁴ have sought to describe and explain the decrease in functional capacity of the lungs and heart resulting from deformities of the chest. Persons so afflicted in youth are usually dwarfed, and their activity is limited. Dyspnea, palpitation and fainting attacks are common symptoms, and tachycardia, low blood pressure and accentuation of the pulmonary second sound are commonly observed. A sudden aggravation of symptoms usually serves as a warning that death is near, for the cardiopulmonary reserve is low. The authors emphasize that depressants of respiratory function, such as morphine, are poorly tolerated and have been known to cause death in patients with severe deformity.

63 van Creveld, S. Glycogen Disease, *Medicine* **18** 1, 1939.

64 Chapman, E. M., Dill, D. B., and Graybiel, A. The Decrease in Functional Capacity of the Lungs and Heart Resulting from Deformities of the Chest. *Pulmonocardiac Failure*, *Medicine* **18** 167, 1939.

GRANULOMATOUS MYOCARDITIS

Jonas⁶⁵ reports his observations in 5 cases in which the myocardium and other tissues were involved in a granulomatous process characterized by tubercle-like foci with giant cells, necrosis and mononuclear cell infiltration. Careful studies did not reveal any evidence to indicate an etiologic relation to tuberculosis or syphilis. The author discusses these 5 cases in relation to somewhat similar cases already on record.

PERIPHERAL VASCULAR COLLAPSE

During 1939 a number of papers have been published by a single group of workers describing their studies on the functioning of the peripheral vascular system.⁶⁶ Their findings are of considerable clinical interest and are important in the diagnosis and proper treatment of peripheral circulatory collapse. These authors have shown that loss of venous tone with consequent pooling of blood is the mechanism responsible for the common type of circulatory collapse. This form of collapse must be distinguished from that which is associated with cachexia or acute loss of blood. The results of their experiments indicate that paredrinol (α -N-dimethyl-p-hydroxyphenethylamine) has as one of its chief actions the elevation of venous tone without at the same time increasing the metabolism of the tissues or causing marked arteriolar constriction. Thus, in cases of shock in which the volume of blood is adequate the administration of paredrinol results in a primary increase in venous tone and an emptying of the splanchnic reservoirs, thereby causing increased venous return to the heart. It is important to point out that in the type of collapse associated with small volume of blood and without venous pooling paredrinol not only is of no value but is contraindicated, as are epinephrine and pitressin, drugs commonly used in the past.

HEART FAILURE AND ITS TREATMENT

It is obviously impossible even to mention by title the large number of worth while articles relating to cardiac failure. Only a few touching on subjects of broad interest have been chosen for review.

65 Jonas, A. F., Jr. Granulomatous Myocarditis, *Bull. Johns Hopkins Hosp.* **64** 45, 1939.

66 Stead, E. A., Jr., Kunkel, P., and Weiss, S. Effect of Pitressin in Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* **18** 673, 1939. Stead, E. A., Jr., and Kunkel, P. Mechanism of the Arterial Hypertension Induced by Paredrinol (α -N-Dimethyl-p-Hydroxyphenethylamine), *ibid.* **18** 439, 1939. Kunkel, P., Stead, E. A., Jr., and Weiss, S. Effect of Paredrinol (α -N-Dimethyl-p-Hydroxyphenethylamine) on Sodium Nitrite Collapse and on Clinical Shock, *ibid.* **18** 679, 1939. Kunkel, P., and Stead, E. A., Jr. Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli, *ibid.* **18** 225, 1939.

The effect of heart failure on the coronary circulation is a factor often neglected or poorly understood. Visscher⁶⁷ ably discusses this effect and points out that fundamentally in all forms of progressive heart failure there are restrictions of the total possible coronary flow. The effects of sudden or gradual occlusion of the coronary vessels are well known, but the restriction of coronary flow produced by elevations in pressure in those cavities into which the coronary venous blood drains is not generally appreciated. Visscher gives experimental data which show that the greater the difference in blood pressure between the aorta and the pulmonary artery the greater the thebesian flow and the less the coronary sinus flow. Also, the greater the difference in blood pressure between the aorta and the coronary sinus, other factors being held constant, the greater the coronary sinus flow. Now it has been shown that the right circumflex artery, which supplies mainly the right ventricular muscle, drains almost exclusively through the right thebesian systems into the right side of the heart. The thebesian flow in the left side of the heart is relatively small, and the blood can reach the left ventricular cavity only during diastole, because only then is the pressure gradient suitable. On the other hand, blood can leave thebesian channels into the right ventricle, both in systole and in diastole, because there is a positive pressure gradient at all times. As a result, it is the right ventricle which will be most seriously affected by a restriction of thebesian flow. Anything which increases right intra-ventricular pressure accelerates heart failure by the restriction of coronary flow which occurs. The author points out the familiar fact that the left side of the heart can carry enormous loads, as in hypertension and in valvular disease, for many years, whereas when the right ventricle works against increased loads the heart may fail rapidly.

The restandardization of digitalis in 1936, increasing its potency, has caused a great deal of confusion not only among pharmacologists but among physicians prescribing the drug. Before this revision the strength was such that ordinarily after a patient was digitalized one pill (1½ grains, or 0.095 Gm.) daily sufficed to maintain its action. In 1936 the United States Pharmacopeial Committee of Revision adopted the international powder as a standard for this country. This has resulted in an increase of from 25 to 30 per cent in the strength of powdered digitalis U. S. P. and of tincture of digitalis U. S. P. The many conflicting reports of the potency of the U. S. P. XI digitalis have been due, according to Edmunds,⁶⁸ to faulty calculation or technic

67 Visscher, M. B. The Restriction of the Coronary Flow as a General Factor in Heart Failure, *J. A. M. A.* **113** 987 (Sept. 9) 1939.

68 Edmunds, G. W. The Potency of Digitalis Preparations of the 1936 Pharmacopeia, *J. A. M. A.* **113** 284 (July 22) 1939.

in standardization. Although there are certain theoretic advantages in international uniformity of such an important drug as digitalis, yet in this country the practical use of $1\frac{1}{2}$ grain (0.095 Gm.) pills has been rendered more difficult. This is so because with routine administration "one pill a day" is often too much. A simple solution might be to reduce the size of the pill. However, as the matter now stands, this fact of increased digitalis potency must be kept in mind.

For many years the administration of digitalis in heart failure with normal rhythm was a controversial matter, especially in England. It is interesting, therefore, to review the investigations of Gavey and Parkinson,⁶⁹ which were undertaken primarily with this question in mind. Sixty-five patients with heart failure and normal rhythm were observed. The control lay in a preliminary rest in bed without digitalis, and, for comparison, another series of 30 patients with heart failure and auricular fibrillation were observed in the same way. The results indicate that 60 per cent of the patients with normal rhythm improved following the administration of digitalis, the improvement was slight in 29 per cent and moderate or marked in 31 per cent. Of the patients with auricular fibrillation, clinical improvement was demonstrated in 72 per cent. If the group with rheumatic heart disease is left aside, the fibrillation series responded to digitalis no better than the normal rhythm series. In other words, the real difference in response of heart failure to digitalis lies not between auricular fibrillation and normal rhythm but rather between rheumatic auricular fibrillation and all other kinds of heart failure irrespective of rhythm. The authors state that digitalis is always indicated in congestive heart failure, irrespective of rhythm, but that it is often inefficient, as it fails completely in about one third of all cases.

Another controversial question regarding the use of digitalis is whether or not it should be given to patients with partial heart block. Blumgart and Altschule⁷⁰ record their observations on 19 patients with congestive failure and partial heart block during digitalization. Of the 19, 11 showed no change in the PR interval, in 7 the PR interval was lengthened, and in 1 it was shortened. In 1 case occasional 2 to 1 heart block disappeared, and in all the rest there were no alterations in the orderly sequence of auriculoventricular contractions. They conclude that digitalis in therapeutic amounts may be safely given in cases of partial heart block but add the warning that caution and careful observation should be exercised.

69 Gavey, C. J., and Parkinson, J. Digitalis in Heart Failure with Normal Rhythm, *Brit Heart J* **1** 27, 1939.

70 Blumgart, H. L., and Altschule, M. D. Should Digitalis Be Administered to Patients with Preexisting Partial Heart Block? *Am J M Sc* **198** 455, 1939.

Boothby, Mayo and Lovelace⁷¹ give the indications for, and the method of administration of, 100 per cent oxygen. They point out that the administration of 100 per cent oxygen will significantly increase the power of the blood to transport oxygen and that it may be given safely in continuous fashion over a period of two days. We should like to call attention to the fact that pure oxygen has been shown to be highly irritating to the respiratory mucosa and that the absence of any symptoms when the "B L B apparatus" (devised by the investigators just mentioned) is used suggests that a concentration of 100 per cent oxygen is not reached.

71 Boothby, W. M., Mayo, C. W., and Lovelace, W. R. One Hundred Per Cent Oxygen. Indications for Its Use and Methods of Its Administration. *J. A. M. A.* **113**: 477 (Aug. 5) 1939.

Book Reviews

Rheumatism By H Warren Crowe, M D (Oxon), B Ch, M R C S, L R C P
Pp 280, with 31 illustrations Price, 12s 6d, cloth London John Bale
Sons & Curnow, Ltd, 1939

It is difficult to write a good book on the subject of rheumatism, and it is almost certain that any book on this subject will provoke argument Dr Crowe has written an excellent book, but it will not meet with universal agreement In writing such a book, one of the most difficult tasks is to arrange a nomenclature so that the writer and the reader may meet on common ground Dr Crowe has met this challenge very skilfully He has drawn on the classifications of the British Commission, the American Commission and the Ministry of Health, with none of which he fully agrees He succeeds well in making his subject matter clear to one who is accustomed to the use of different terms

After dealing with the matter of nomenclature, he continues with a discussion of differential diagnosis, pathology and etiology This is well done and is quite orthodox until the section on etiology is reached All are familiar with Dr Crowe's ideas about the infectious nature of rheumatism, and these ideas are fully expounded in the section on etiology The ideas are of course carried over into the discussion of treatment in which the author's original work in vaccine treatment is discussed

There are additional chapters on physical therapy, roentgen ray therapy and the orthopedic treatment of rheumatism The concluding chapter deals with laboratory technic and the technic of physical therapy

This book may be recommended as a carefully constructed piece of work that is the result of long and careful observation of many patients who have suffered from this disease The author mentions the "nebulous conception of rheumatism" This work will no doubt serve as one of the instruments to dispel the cloud that surrounds the subject

Failure of the Circulation By Tinsley R Harrison, M D, Associate Professor of Medicine, Vanderbilt University School of Medicine Second edition
Price, \$4.50 Pp xiv + 502, with 59 figures and 22 tables Baltimore
The Williams & Wilkins Company, 1939

The first edition of this book was published in 1935 It was deservedly successful A reviewer (*J A M A* **105** 1141 [Oct 5] 1935) remarked that the book presented clinical cardiologists with the latest applications of the altered physiologic function in heart failure and recommended that all internists read it The review in the *ARCHIVES OF INTERNAL MEDICINE* (**57** 643 [March] 1936) was equally complimentary Here it was said that the book not only discussed the theoretic aspects of heart failure in a thoroughly satisfactory manner but also contained a great deal of practical advice concerning the diagnosis and treatment of heart disease It was an authoritative treatise Both reviews were the leading ones in the issues of the periodicals in which they appeared

The second edition follows the general pattern of the first, with certain modifications, and is a trifle over a hundred pages longer The author has been careful as to how his book was allowed to grow He has made a conscientious effort to strengthen the first edition in all its weak spots Most of the extra pages, however, are due to new ideas The increased length of the book reflects very clearly the activity of workers in the field of cardiology and the rapidity with which new knowledge has been built up

Once more this book deserves high praise Like the first edition, the second presents clinical cardiologists with the latest applications of the physiologic conceptions of heart failure Cardiologists, students and practitioners all will find it interesting, informative and stimulating

Medizinische Praxis Sammlung für ärztliche Fortbildung Volume 27
 By M. Ratschow Mit einem Geleitwort von R. Cobet Price, 975 marks
 Pp 193, with 46 illustrations Dresden Theodore Steinkopff, 1939

This most recent (twenty-seventh) volume of the "Medizinische Praxis" series is concerned with peripheral vascular disturbances. After briefly defining these conditions and succinctly reviewing their historic development, the author describes the anatomy and physiology of peripheral blood vessels. A fairly complete consideration of the various diagnostic methods used in studying the organic and functional changes in the peripheral vessels is presented. The characteristic clinical manifestations of the various types of peripheral vascular diseases are described and their management stated. Obviously, completeness of detail cannot be achieved in a short monograph on a subject the literature of which has now assumed voluminous proportions. Thus a mere paragraph on thrombophlebitis is woefully inadequate. However, the book serves as a quick reference for the student and general practitioner. There are forty-six illustrations, consisting of charts, diagrams, photographs, photomicrographs and arteriograms. An incomplete but fairly representative and up-to-date bibliography is included. There is also an author and a subject index.

Annual Review of Physiology, Volume 1 Editor, J. Murray Luck and
 associate editor, Victor E. Hall Price, \$5.00 Pp 709 Stanford University,
 California Stanford University Press, 1939

The need for reviews and compendia of medical literature becomes more and more evident each year. Volume 1 of the *Index Medicus*, in 1927, contained 820 pages, whereas volume 20, in 1936, had extended to no less than 1499. The "Annual Review of Physiology," of which the first volume has recently appeared, seems therefore to be inevitable, and one is pleased to find that Murray Luck, veteran of the Annual Review of Biochemistry, is in charge also of this latest physiologic review. Twenty-four articles by authorities in the various branches of physiology fill a volume of some 700 pages. As many as four or five hundred references follow some of the articles. My only criticism—or rather comment—is that in some of the contributions the material is so condensed that it makes poor reading, and the volume is really a succession of abstracts, but when a year's output of work is condensed into one volume this is hardly to be avoided.

INSULIN AND CEREBRAL DAMAGE

F KLEIN, M D

AND

J A LIGTERINK, M D

GRONINGEN, NETHERLANDS

Hypoglycemia manifests itself chiefly by symptoms due to disturbances of the autonomic and central nervous systems. In their monographs Sigwald¹ and Wilder² gave detailed descriptions of all neurologic and psychic symptoms to be noted during a hypoglycemic state, and it may be stated without hesitation that there is no neurologic or psychic abnormality which has not been observed either separately or in combination. Given susceptibility of the central nervous system to insulin, it is surprising that fatal damage of the central nervous system so seldom occurs in sufferers from diabetes treated with insulin. In 1932 Sigwald¹ gave short descriptions of 24 cases of fatal hypoglycemic coma known to him. In addition, Rathery³ reported a very instructive fatal case in 1938.

Fortunately, however, the fatal cases are rare. The hypoglycemic symptoms as a rule disappear when the blood sugar has been raised to the normal level through the administration of sugar. Sigwald and Wilder only incidentally mentioned disturbances persisting after the administration of sugar. Sigwald described a number of patients with chronic mental disturbances. During the last few years, moreover, various cases of serious, chronic disturbances of the brain have been reported, some of which ended in death.

The syndrome of hyperinsulinism is well known, especially through the reports of the American investigators (Harris,⁴ Wilder,⁵ Ryneal-

From the Sanatorium "Rustoord," Apeldoorn, Netherlands

1 Sigwald, J. *L'hypoglycémie*, Paris, Gaston Doin, 1932

2 Wilder, J. *Klinik und Therapie der Zuckermangelkrankheit*, Vienna, Verlag für Medizin, Weidmann & Co, 1936

3 Rathery, F. *Le diabète sucré. Leçons cliniques (1936-1937)*, Paris, J. B. Baillière et fils, 1938

4 Harris, L. The Diagnosis and Treatment of Hyperinsulinism, *Ann Int Med* 10 514, 1936

5 Wilder, R. M. Spontaneous Hypoglycemia, *Internat Clin* 46 143, 1936

son and Moersch,⁶ and others) In 1938 Malamud and Grosh⁷ published, in connection with a report on a patient suffering from pancreatic adenoma, an extensive survey of the literature on this syndrome During that patient's life many psychic and neurologic symptoms were observed, and at autopsy extensive irregularities of the central nervous system were found

The insulin shock therapy of Sakel has led to the observation of all kinds of cerebral complications With this therapy the patient is brought into a deep coma Usually the coma is interrupted after one to one and a half hours by peroral or intravenous administration of dextrose Full consciousness is recovered as a rule within a half hour There are numerous cases, however, as any one who applies this therapy will have experienced, in which consciousness does not return so soon Here a distinction should be made between

- 1 A delayed recovery of consciousness, during which, in addition to various forms of hyperkinesia, disturbances of speech and periods of exaltation, serious respiratory and pulse abnormalities may occur (Golden⁸)
- 2 A persistence of the comatose state, lasting from a few hours to several days, after which consciousness gradually returns (Salm⁹) Not seldom many weeks or even months may elapse before the neurologic and psychic symptoms may be said to have totally disappeared Plattner¹⁰ and Milch and Bolles¹¹ described a case in which Korsakoff's syndrome occurred and persisted for several months Pap,¹² who as early as 1936 gave an excellent description of the syndrome of Sakel's insulin treatment, described in detail 2 cases of prolonged coma, in the course of and following

6 Ryneerson, E. H., and Moersch, F. P. Neurologic Manifestations of Hyperinsulinism and Other Hypoglycemic States, *J. A. M. A.* **103** 1196 (Oct 20) 1934 Carlson, L. A., and Ryneerson, E. H. An Unusual Case of Spontaneous Hypoglycemia, *Proc. Staff Meet., Mayo Clin.* **12** 486, 1937 Ryneerson, E. H., and Walters, W. An Unusual Case of Spontaneous Hypoglycemia, *ibid.* **13** 728, 1938

7 Malamud, N., and Grosh, L. C., Jr. Hyperinsulinism and Cerebral Changes. Report of Case Due to Islet Cell Adenoma of Pancreas, *Arch. Int. Med.* **61** 579 (April) 1938

8 Golden, L. A. Neurologic Manifestations in "Hypoglycemic Shock" (Sakel), *Ann. Int. Med.* **11** 819, 1937

9 Salm, H. Benommenheitszustände im Anschluss an die Insulinschockbehandlung von Schizophrenen, *München med. Wchnschr.* **84** 1046, 1937

10 Plattner, P. Amnestisches Syndrom nach Insulin-Cardiazol-Behandlung, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **162** 728, 1938

11 Milch, E. C., and Bolles, M. M. A Case of Prolonged Coma Following Insulin with Eventual Recovery, *J. Nerv. & Ment. Dis.* **88** 817, 1938

12 Pap, Z. Erfahrungen mit der Insulinschocktherapie bei Schizophrenie, *Monatschr. f. Psychiat. u. Neurol.* **94** 318, 1936

which serious disturbances of the pyramidal and extrapyramidal tracts, cramps and motor aphasia, combined with abnormalities of temperature, pulse and respiration, were noted. After administration of dextrose the different symptoms in all their variety may be observed just as prior to the onset of the comatose state. Not always, however, is there a total recovery. Schraagen¹³ observed chronic disturbances of the brain.

- 3 An uninterrupted coma followed by death after a shorter or longer period (Muller¹⁴, Leppien and Peters¹⁵, Salm⁹, Timmer¹⁶, Kastein,¹⁷ Cammermeyer,¹⁸ MacKeith and Meyer¹⁹). Although in some cases (an instance was observed by us but is not commented on in this report) extensive pulmonary and other abnormalities have been found at autopsy, the existence of a serious disturbance in the functions of the central nervous system is here absolutely undeniable.

During the last few years cases have been reported of permanent damage of the brain in patients suffering from severe diabetes who required large doses of insulin and in whom a continuous appearance of hypoglycemic symptoms could not be avoided. The syndromes in these patients bear a close resemblance to those seen after prolonged coma in patients given Sakel's therapy.

Fenz and Kogerer²⁰ described the case of a 16 year old boy who had suffered from serious diabetes from his fourth year onward and who during the last fifteen years frequently had hypoglycemic symptoms. He was given 100 units of insulin per day. Dulness and obliviousness had been observed for five months when he was admitted to the hospital in a serious hypoglycemic coma with many epileptic seizures. After he recovered consciousness the patient showed for a fortnight a syndrome

13 Schraagen, J. C. Case of Dementia Developing After Insulin Shock Therapy of Schizophrenia, *Psychiat en neurol bl* **42** 373, 1938.

14 Muller, M. Die Insulintherapie der Schizophrenie, *Schweiz Arch f Neurol u Psychiat (supp)* **39** 9, 1937.

15 Leppien, R., and Peters, G. Todesfall infolge Insulinshockbehandlung bei einem Schizophrenen, *Ztschr f d ges Neurol u Psychiat* **160** 444, 1937.

16 Timmer, A. P. Death During Treatment of Schizophrenic Patient with Insulin Shock According to Sakel Method, *Nederl tijdschr v geneesk* **82** 3088, 1938.

17 Kastein, G. W. Insulinvergiftung. I. Klinische und pathophysiologische Beschreibung, *Ztschr f d ges Neurol u Psychiat* **163** 322, 1938.

18 Cammermeyer, J. Ueber Gehirnveränderungen, entstanden unter Sakelscher Insulintherapie bei einem Schizophrenen, *Ztschr f d ges Neurol u Psychiat* **163** 617, 1938.

19 MacKeith, S. A., and Meyer, A. A Death During Insulin Treatment of Schizophrenia, with Pathological Report, *J Ment Sc* **85** 96, 1939.

20 Fenz, E., and Kogerer, H. Hypoglykämie und Schizophrenie, *Jahrb f Psychiat u Neurol* **54** 241, 1937.

characterized by negativism, catalepsy, grimacing and motor restlessness. Subsequently improvement gradually set in, after four months, however, apathy and dulness still persisted.

Helland-Hansen²¹ described the case of a woman aged 33 who had been suffering for eight years from severe diabetes and who was given 212 units of insulin daily. While she was in a hypoglycemic coma, mistaken by the family doctor for hyperglycemia, she was given 160 units of insulin subcutaneously and 160 units intramuscularly. The coma persisted for three days, during which Cheyne-Stokes respiration, clonic cramps and reflex changes were observed. Then for nine days there existed a dream state, with symptoms of parkinsonism, tremor, perspiration, a masklike face and slowness of thought. Later improvement occurred, but after seven months the patient was still an invalid and had to be accompanied when going out. Labbe and Boulin²² described a case characterized principally by neurologic irregularities. They observed a patient 33 years of age who in addition to hypoglycemic coma presented hemiplegia and aphasia of the right side. Aphasia was still present after two months. They believed they were justified in definitely excluding a primary vascular disturbance.

Also, in diabetic patients treated with protamine zinc insulin, the hypoglycemic symptoms, once they have occurred, have not seldom been seen to disappear only after some hours or sometimes only after some days, in spite of the fact that the blood sugar has been at normal levels for some time. In these cases it should be assumed that the protamine zinc insulin had an unfavorable influence on the central nervous system. The fact that protamine zinc insulin can keep the blood sugar at abnormally low levels for many hours points to a danger for the central nervous system. The already rather high percentage of patients treated with protamine zinc insulin who have died of hypoglycemia points in the same direction.²³

We shall now report 2 cases of serious damage to the brain. The first case was that of a schizophrenic patient in whom a complication occurred during administration of the therapy of Sakel, the second was that of a psychically sound diabetic patient treated with regular and protamine zinc insulin who remained in a comatose state for many days.

21 Helland-Hansen, B. Psychose nach Insulinvergiftung, *Norsk mag f lægevidensk* **98** 1306, 1937.

22 Labbe, M., and Boulin, R. Les accidents hemiplegiques au cours de l'insulinothérapie, *Presse med* **45** 225, 1937.

23 Danger of Protamine Insulins, editorial, *J A M A* **111** 254 (July 16) 1938. Wilder, R. M. Disease of Metabolism and Nutrition. A Review of Certain Recent Contributions, *Arch Int Med* **59** 329 (Feb.) 1937. Boller, R., and Pilgerstorfer, W. Die Hypoglykämie bei Protamin-Zink-Insulinanwendung, *Klin Wchnschr* **17** 1065, 1938. Groen, J., and Garré, A. H. Death Due to Hypoglycemia During Treatment with Protamine Zinc Insulin, *Nederl tijdschr v geneesk* **83** 1844, 1939.

Although the blood sugar of the diabetic patient had not been determined during the initial days of the coma, the syndrome resembled that of the schizophrenic patient, as well as the syndromes observed in other patients described in the literature on the subject, to such an extent that we believe we may confidently call the case an instance of hypoglycemic damage to the brain

REPORT OF CASES

CASE 1—K Z, a man aged 25, a German refugee and merchant's apprentice, was admitted to the sanatorium March 7, 1938. He refused to learn a trade and gave as a motive that he was a great singer. During the first months of 1938 he voiced paranoid ideas, viz, that he was forced to marry against his will, that at night he was narcotized, that his fillings were being pulled from his teeth, that he was being poisoned with anthracite put in his cocoa. In the street he exposed himself, thinking "they" wanted to turn him into a girl. On admission to the sanatorium his behavior was theatrical, he suddenly cried out, thinking that he was being murdered. He was strongly cataleptic and gave way to senseless screaming fits and catatonic states of agitation. On physical examination, including studies of the blood, urine and cerebrospinal fluid, no abnormalities were found. Wassermann tests of the blood and cerebrospinal fluid were negative. His condition was diagnosed as schizophrenia.

In April 1938 Sakel's insulin shock treatment was started. On the fifth day of treatment coma set in, on the administration of 80 units of insulin. By the twenty-fourth day of treatment the patient had been in coma seventeen times. Prior to becoming comatose he was always very restless, while comatose he had tonic cramps. The coma on the twenty-fifth day of treatment, after 90 units had been administered, resembled the previous ones, but the patient did not recover consciousness after oral administration of dextrose. Neither intravenous administration of dextrose nor injection of epinephrine hydrochloride gave a better result, although the level of the blood sugar was raised to 220 mg per hundred cubic centimeters. Lumbar puncture did not produce improvement either. The temperature was 40.8 C (105.4 F), the pulse rate, 200. Electrocardiographic examination revealed sinus tachycardia. The blood pressure was 140 systolic and 70 diastolic, the respirations were 46 per minute and fairly regular. There were occasional myoclonic spasms in the face and there were movements of the arms and legs. Babinski's sign was present on the right side, tendon reflexes were present. The therapy consisted in intravenous injection of 200 mg of theophyllineethylenediamine. The comatose state still persisted. The corneal and pupillary reflexes were present. In the evening he was calmer, the pulse rate was 140 and the temperature 39.7 C (103.4 F).

The next day, May 26, the condition remained the same. The pulse rate was 120 and the temperature was 38.8 C (101.8 F), the respiratory rate was 28. There were constant slight myoclonic spasms and swinging movements of the limbs. The tendon reflexes were normal. The abdominal and cremasteric reflexes were absent. There were no signs of meningeal irritation. Babinski's sign was present on the right side. No obvious abnormalities of the fundus oculi were observed. The cerebrospinal fluid was normal. The sugar metabolism was disturbed. There was sugar in the urine, with albumin and casts. The therapy consisted in intravenous administration of a hypertonic solution of sodium chloride. The patient was fed by an oral tube a diet rich in vitamin B complex. On May 27 the comatose state was a little less profound, there was a reaction on pain stimulation, and Babinski's sign had disappeared. Herpes labialis developed. On May 28 the patient was somnolent.

When his name was called, he hardly woke up. Feeding was no longer artificial. There was a lowering of the temperature. On May 29 ptosis of the left eye appeared, also strabismus and somnolence. Clinically there was a great resemblance to the syndrome of severe encephalitis. The therapy consisted in intravenous injection of a 40 per cent solution of methenamine. On May 31 the more consciousness returned the greater his restlessness became. There were typical rolling movements along the body axis, accompanied by digging of the head into the pillows and swinging movements of the limbs. The condition bore slight resemblance to chorea. There was continuous salivation. He obviously could not pronounce a single word, but he uttered some unintelligible sounds.

On June 8 he had fits of crying and many symptoms of Parkinson's syndrome. The forearms were rigidly flexed and the head bent, alternated by ballistic and rolling movements of the body. Salivation continued, ptosis disappeared, the cremasteric reflexes returned, the abdominal reflexes were still absent. His behavior was noncooperative. On June 10 the patient uttered a few words. In bed he

TABLE 1—Laboratory Data of the Urine and Blood (Case 1)

Date	Albu min	Reaction	Sediment	Sugar, %	Blood Sugar		Comment
					Mg in 100 Cc	Hour	
5/25/38					223 81	3 p m 5 p m	After intravenous in- jection of dextrose
5/26/38	++	Acid	Some erythrocytes, some leukocytes, many hyaline casts	1.8	154	10 a m	
5/27/38	1 ‰*	Alkaline	Some erythrocytes	0.75	192	5 p m	
5/28/38	1 ‰	Acid	Some hyaline and some granular casts	2.5			
5/29/38	¾ ‰	Alkaline	Three leukocytes	2.5			
5/30/38	½ ‰	Alkaline	Some casts	0.7	114 before eating		Only a few urine specimens could be examined
6/ 3/38					113 before eating		
6/10/38	Trace	Alkaline			101 before eating		
6/20/38		Alkaline			70 before eating		

* ‰ indicates parts or grams per thousand or per liter

always had the same typical rolling and swinging movements. Sucking and biting reflexes appeared as soon as any object was made to touch his mouth. He could not take food without assistance. On June 20 he pronounced his name and was able to tell time by his watch. There remained persistent incontinence of feces and urine. On June 23 his walking was ataxic, he could not write or read, showed paraphasia, motor and sensory aphasia and slept much. On June 28 he had echolalia, no notion of time and place and a disturbed memory. Polyphagia developed. He ate whatever was put before him, even tobacco, grass and wood wool. Sucking and biting reflexes were present, and the abdominal reflexes returned.

On July 7 psychologic examination revealed motor and sensory aphasia, agraphia, tactile agnosia, alexia and extreme amnesia. The higher psychic functions had disappeared. Only a few strongly automatized fragments of former knowledge were still present.

On August 12 he had persistent alexia, his memory improved and the aphasia disappeared. The motor functions were slightly disturbed. His behavior was infantile, with faulty speech and permanent masturbation.

On September 17, the intellectual level, experimentally ascertained, was that of a child of 8.

On April 16, 1939, the greater part of the motor functions had been recovered. Alexia, which of all disturbances had been the most severe and the most persistent, had now disappeared. The intellectual functions appeared experimentally to have been, for the most part, recovered. Relative to the period from February to September 1938 there was total amnesia. Remnants of megalomania could still be observed, as well as disturbances of judgment. The infantile behavior persisted. Roentgenograms of the skull were normal.

Laboratory Data—In table 1 a number of data from examinations of the urine and blood have been combined. During the first days there was a disturbance of the sugar metabolism, i e., hyperglycemia and glycosuria. This disturbance soon disappeared, however, and made way for a contrasting picture, viz., a

TABLE 2—*Laboratory Data on the Blood (Cases 1 and 2)*

Date, 1938	Plasma Chlorides as Sodium Chloride, Mg. in 100 Cc	Nonprotein Nitrogen, Mg. in 100 Cc	Corpuscular Volume, %	Cholesterol, Gm per 100 Cc	White Blood Cells						Sedimentation Rate	Fibrinogen
					Total	Eosinophils	Basophils	Nonsegmented	Segmented	Lymphocytes	Monocytes	
Case 1												
5/25	582	38	50.9		17,000			2	86	12		
5/26	553				16,300							
5/27	588*	40						8	49	37	6	
5/28					13,600	3	1	3	54	37	2	
5/30	564	31	48.4		8,600	1	1	5	38	50	5	
6/ 2					13,100	2	1	3	58	34	2	64
6/ 9	571	26	49.3	160	9,900							48
6/16					10,600	2	1	2	44	44	7	
6/27	567				9,400	1		3	43	49	4	16
7/ 4	560	24	47.1	320	7,100	5			44	50	1	8
9/ 5	589			250	5,300	3		1	62	33	1	5
Case 2												
2/16						1	1	3	54	38	3	5
6/15		Urea, 100										
6/18					8,600			8	77	7	8	20
7/19					5,800	2		3	63	29	3	9
7/24	555	Urea, 56	52.7	280	6,500	2		1	69	27	1	6
8/17	563	Nonprotein Nitrogen, 23	54.7		4,900							3
10/20	580	Urea, 31	51.5		5,000	2		4	69	22	3	

* During treatment with sodium chloride

low sugar content and only a slight increase after administration of 100 Gm of dextrose. For instance, the blood sugar curve taken on July 4 showed the following values: 68 mg per hundred cubic centimeters before 100 Gm of dextrose was administered, at one-half hour after the administration of dextrose, 119 mg, at one hour, 107 mg, at one and one-half hours, 98 mg, at two hours, 56 mg, at three hours, 80 mg, at four hours, 84 mg, and at five hours, 89 mg. This curve was determined during a period in which the patient ate and drank a good deal, eating often as much as sixteen slices of bread in the morning and voiding 2½ liters of urine on an average. The cholesterol content of the blood increased from 160 mg per hundred cubic centimeters on June 9 to 320 mg on July 4. The laboratory data on the blood have been summarized in table 2. During the first week there was a slight increase in the nonprotein nitrogen content. The chloride content was constantly fairly low. During the comatose state there was a rather marked leukocytosis, with lymphopenia and an absence of monocytes on the first day and with an increase of nonsegmented neutrophils and lymphocytosis with 6 per cent monocytes on the third day, eosinophil cells were not observed before the

fourth day The number of leukocytes decreased to normal in the month of June Lymphocytosis persisted The initial strongly increased rate of sedimentation of the erythrocytes also gradually subsided to normal With few exceptions, repeated examination of the spinal fluid (table 3) showed normal values The blood pressure, which had not been taken on the first day, still showed an increase on the second day, 230 mm, later it subsided to normal The chloride content on the first day was high, 783 mg of sodium chloride per hundred cubic centimeters This certainly was abnormal in proportion to the chloride content of the blood plasma, 582 mg of sodium chloride per hundred cubic centimeters The lumbar puncture was made fifteen minutes after taking the blood pressure

Summary—A patient who was being treated for schizophrenia with insulin was not awakened from the coma produced by administering 90 units of the drug, notwithstanding a copious supply of sugar and a

TABLE 3—*Laboratory Data on the Cerebrospinal Fluid (Cases 1 and 2)*

Date, 1938	Appear- ance	Cells per 3 Cu Mm	Protein, Mg in 100 Cc			Non protein Nitrogen, Mg in 100 Cc	Chlorides as Sodium Chloride, Mg in 100 Cc	Initial Pressure, Mm	Sugar Mg in 100 Cc
			Total	Albumin	Globulin				
Case 1									
3/24	Clear	13	25.7	22.8	2.9	Colloidal gold and mastic reactions normal			
5/25	Clear	13	17.4	14.5	2.9	17	783		55
5/26	Clear					21	791*	230	115
5/28	Clear		13	11.6	1.4	Colloidal gold and mastic reactions normal			125
5/29	Clear	3	14.5	13.1	1.4	23	741	150	
6/9	Clear	2				14	735		
Case 2									
6/16	Clear	6	30.4			Colloidal gold and mastic reactions normal			200
6/23	Clear	7	33.4	20.3	13.1			180	
7/28	Clear	8	30.4	15.9	14.5		732	120	
8/29	Clear	2	18.8	14.5	4.3	15	702		

* After intravenous injection of sodium chloride

normal blood sugar content After three days of coma, consciousness gradually returned In addition to fever, tachycardia and tachypnea, extensive neurologic and psychic symptoms were recorded which persisted for many months

CASE 2—A laundryman now 22 years of age entered Juliana Hospital, Apeldoorn, in a state of coma on July 15, 1938 During April 1936 he had been nursed in the same hospital on account of a pelvic and left femoral fracture sustained in a motorcar accident On that occasion he had not been unconscious In the past he had always been healthy Thirteen days after the accident the patient started drinking great quantities of water and urinating much and frequently No dextrose was found in the urine during the first five days after the accident On the thirteenth day, however, 200 Gm of dextrose was excreted With the patient on a regimen of 15 and 10 units of regular insulin the urine could easily be freed from dextrose In July the patient started working again

In March 1937 he entered the medical department of the Utrecht University Clinic (Prof Hymans v d Bergh) as for the last few months he had been very thirsty again and had excreted a high percentage of dextrose in the urine It

appeared very difficult to regulate his sugar metabolism. While on the one hand the blood sugar rose very quickly after the injection of carbohydrate without insulin and the blood sugar during fasting was very high, often as much as 500 mg per hundred cubic centimeters, on the other hand there existed a great sensitivity to insulin. Several times there were hypoglycemic manifestations. After five months the patient left the clinic on a diet of 160 Gm of carbohydrate and 30, 10 and 25 units of insulin per day.

In the middle of February 1938 he reentered the clinic on account of emaciation and increasing glycosuria. The administration of protamine zinc insulin was instituted at once. It appeared possible to control his sugar metabolism satisfactorily with 40 units of protamine zinc insulin in the morning and 20 units of unmodified insulin in the afternoon. The excretion of sugar ranged from 0 to 40 Gm of dextrose per day. He left the clinic on April 23 and returned to work.

On Sunday morning, June 12 the patient took his insulin as usual at 7:30. His family did not notice anything unusual. He told them he was going back to bed but that he would come down to breakfast in half an hour. He did not reappear, however, and his family found him lying against his bed, dazed and sleepy. He still uttered some words to the effect of wanting to eat his porridge, but he became more and more dazed. A physician was sent for. On the latter's arrival the patient was in a subcomatose state. He did not perspire, his mouth secreted a mucous fluid. The physician injected 60 units of insulin. Total coma set in, which lasted for many days. On the evening of June 12 the physician injected 40 units of protamine zinc insulin, the next day he injected 20 units supplemented by 40 units of unmodified insulin, and, as acetone (no dextrose) was found in the urine, he administered sodium bicarbonate and dextrose per rectum. No other food was given. The next day the physician again administered 20 and 40 units of insulin, 3.5 Gm of sugar per hundred cubic centimeters having been found in the urine at the time. The following day he gave the patient 20 units of insulin twice. On admission to Juliana Hospital that night the patient was in deep coma. Examination by Dr. Rodbard, director of the hospital, revealed that his pulse and respirations were normal, there was no question either of Kussmaul's or of Cheyne-Stokes respiration. The skin was dry, with many spots of decubitus. The tonus of the bulbus oculi was normal and the tonus of the muscles of the extremities was lowered. The patient did not react to pain stimulation. The reflexes of the corneas and pupils were present. Around the mouth there were, as usual in hypoglycemic states, peculiar fibrillary contractions. There were no signs of meningeal irritation and no abnormalities of the lungs and heart. The abdomen was sunken, and the abdominal reflexes were absent. The reflexes of the lower extremities were weak, Babinski's sign was present on both sides. The temperature mounted to 37.8 C (100 F), the blood sugar to 320 mg and urea to 100 mg per hundred cubic centimeters. The urine revealed 5 per cent dextrose, the test for acetone was positive, that for diacetic acid was negative. The test for albumin was slightly positive. The patient was incontinent of feces and urine. The treatment consisted in intravenous injection of sugar, administration of insulin and hypodermoclysis of physiologic solution of sodium chloride.

The next day the coma was a little less profound, the patient was rather restless and made choreatic and athetotic movements with his arms. The fundus oculi was normal and the cerebrospinal fluid was clear and almost normal. During the following days a slight improvement was observed. The patient reacted on pain stimulation, he made sucking movements when the corners of his mouth were touched with a finger and he swallowed liquid poured into his mouth.

Toward the end of June he became a little more lively, but otherwise his condition remained the same. He behaved like a complete idiot. He did not talk but continuously uttered bestial sounds. Thus it became necessary to send him to the asylum for patients with mental disease, Apeldoornsche Bosch. He stared vacantly, did not take any notice of his surroundings, did not react on being called and did not follow either light or people. He slobbered and made continual gnawing movements, he ate greedily, gnawed at the bedside and continued to be incontinent of feces and urine. This condition has continued up to the time of writing, there is only very slight improvement. At present the patient follows people who walk around his bed, but he does not recognize food when

TABLE 4—*Blood Picture During Induced Hypoglycemia*

Date	Hour		Total		Percentages						Blood Sugar, Mgr per 100 Cc
			Leukocytes	Eosinophils *	Eosinophils	Basophils	Nonsegmented	Segmented	Lymphocytes	Monocytes	
Patient A, ♂, 27 yr old											
11/23/38	7 30 a m	Before injection of 340 units insulin	6,900	600	2	1	2	58	34	3	99
	10 30 a m	Precoma	9,300	200	0	0	2	71	26	1	55
	12 30 a m	Coma	14,600	50	0	0	6	78	16	0	41
	5 30 p m	4 hours after the end of coma	12,000	200	0	0	1	59	38	2	112
11/24/38	7 30 a m		8,400	400	5	0	1	64	26	4	102
Patient B, ♀, 23 yr old											
12/ 5/38	7 30 a m	Before injection of 320 units insulin	10,400	500	5	0	2	54	35	4	
	1 00 p m	Coma	28,100	3†	0	1	3	89	5	2	
	6 00 p m	4 hours after the end of the coma	10,600	6†	1	0	3	78	17	1	
12/ 6/38	7 30 a m		11,300	400	4	2	2	56	33	3	
Patient C, ♂, 32 yr old											
10/14/38	7 30 a m	Before injection of 220 units insulin	4,400	500	12	0	0	50	36	2	
	11 30 a m	Coma	13,200	50	1	0	2	81	15	1	
	4 30 p m	4 hours after the end of coma	9,600	100	2	1	2	74	20	1	
10/16/38	8 30 a m		4,600	600	6	1	1	30	60	2	

* Method of Friedman (J A M A 103 1618 [Nov 24] 1934)
† Total in counting chamber

it is held before his eyes. He can walk, however, in a very ataxic manner. The reflexes of his abdomen have returned, and the positive Babinski and Chaddock signs on the left, which persisted longest, have disappeared, as have the sucking reflexes. But another serious symptom has manifested itself. The patient suffers regularly from epileptic convulsions, sometimes of the jacksonian variety, alternately beginning on the right and on the left side.

Often, on account of such an epileptic state, it has become necessary to administer somnifen (a mixture of the diethylamine salts of diethylbarbituric acid and allylisopropylbarbituric acid) intravenously. However, a roentgenogram of the skull revealed no abnormalities. The controlling of the sugar metabolism of this patient, who still is very sensitive to insulin and whose blood sugar rises quickly without insulin, has caused new difficulties. He repeatedly refuses food after having received an injection of insulin a moment before. Often he vomits what he has been fed artificially, especially during the days following convulsive

seizures. All sorts of neurologic irregularities have developed, and a number of times Cheyne-Stokes respiration for a long period. A correlation between the lowering of the blood sugar and the convulsive seizures could never be proved, however. The question that remains to be answered is why the patient lapsed into coma on June 12. We believe that the blood sugar values during fasting in the month of April may give an explanation. While in the first five days of April the values amounted to 300, 262, 346, 344 and 170 mg per hundred cubic centimeters, these figures were 185, 91, 226, 110 and 106 mg per hundred cubic centimeters in the last days before the patient left the hospital, a curve which is considerably lower. The tendency toward a lowering of the blood sugar still persisted after his dismissal from the hospital, until at last hypoglycemic symptoms manifested themselves.

Laboratory Data—Results of examinations of the blood and of the spinal fluid are summarized in tables 2 and 3. As the patient received little liquid during the first three days of coma, the urea content of the blood was increased to 100 mg per hundred cubic centimeters. After the administration of liquid the urea content decreased rapidly. It is true that the hematocrit value remained slightly increased. This was due to polyuria. There was constant excretion of sugar. This also accounts for the low chloride values. On the sixth day the blood, with a normal quantity of leukocytes, showed a shift to the left, 8 per cent of the cells being monocytes, without any eosinophil cells. In the spinal fluid a slight increase in cells and globulin was revealed, which disappeared after three months. The Wassermann reactions of the blood and spinal fluid were negative.

Summary—A diabetic patient treated with regular and protamine zinc insulin was found in a comatose state and was given another 60 units of regular insulin. The coma persisted for six days, after which several functions were gradually recovered, viz., eating, laughing, crying, emitting inarticulate sounds, defense against pain stimulation and, finally, standing up and ataxic walking. All signs of rational thinking, higher feelings and reasoned actions remained absent. Briefly, the intellectual level finally reached by the patient was that of a complete idiot. The entire mental picture became that of an animal.

COMMENT

The symptoms occurring in both patients were strikingly similar. During the comatose state there were myoclonic spasms in the face and movements of the upper extremities similar to those of patients with chorea and athetosis. Of the neurologic disturbances, Babinski's sign and the absence of the abdominal reflexes persisted longest. In both patients sucking and biting reflexes, as well as polyphagia and salivation, occurred. The spinal fluid contained nothing abnormal. The irregularities in the first patient were of a passing nature, whereas those in the second were serious and chronic. At this point we may elaborate a few of the irregularities observed.

1. The postcoma disturbance of the sugar metabolism in case 1 has been described also by Kasten¹⁷. Lups²⁴ observed that the longer the

24. Lups, S. Glucosurie nach Insulinkoma. *Klin. Wchnschr.* **17**: 207, 1938.

coma ensuing from Sakel's insulin therapy is allowed to continue the more the glycosuria occurring after administration of an equal amount of dextrose increases. It was his opinion that this is due to a disturbance of the liver. In our opinion, however, the cause should be sought for in a cerebral disturbance.

2 In case 1 fairly marked albuminuria was found during one week, in case 2 only a slight trace of albumin could be observed in the urine.

3 The very extended occurrence of herpes labialis in case 1 must be mentioned separately. Pap¹² reported this symptom in one of his patients.

4 In both cases, during the coma the blood picture presented a shift to the left with absence of eosinophils, and in the first case, leukocytosis as well. A similar blood picture has been noted in other cases of induced hypoglycemia, but only for a short time, during the coma and a few hours after consciousness had been fully restored through the administration of dextrose (table 4). In the case studied by Malamud and Grosh,⁷ too, no eosinophil cells were observed during a serious hypoglycemic state.

SUMMARY AND CONCLUSIONS

A schizophrenic patient in whom coma was produced by the administration of 90 units of insulin recovered consciousness only after three days, in spite of a normal and even increased content of sugar in his blood. During this period and following it there occurred, in addition to neurologic and psychic symptoms, irregularities in the sugar and water systems, also initially a high temperature, tachycardia and tachypnea. Most of these symptoms disappeared after one year.

A diabetic patient without psychic abnormalities, who was treated with regular and protamine zinc insulin, became comatose and was given 60 units of insulin. After a coma of six days a slight improvement took place. Extensive neurologic disturbances were observed. The intellectual level reached by the patient was that of a complete idiot. Because of the great similarity in the symptoms of the two patients it is our contention that cerebral damage caused by insulin-induced hypoglycemia must be assumed to have occurred in the second patient as well, in spite of the lack of data on the blood sugar values during the first days of the comatose state.

Thus, the danger to the brain ensuing from Sakel's technic and from the treatment of diabetic patients with insulin and protamine zinc insulin should not be underestimated.

Prof de Langen, Dr Kulst, Dr Rodbard and Dr Simons provided the details from the clinical records in case 2.

DISSECTING ANEURYSM OF THE AORTA

JOHN A REISINGER, M D

WASHINGTON, D C

It is stated in the 1928 edition of Osler and McCrae's textbook¹ that "dissecting aneurysm is uncommon. There were only two cases in sixteen years at the Hopkins' Hospital where aneurysm is exceptionally frequent." Professor Shennan, in a monograph,² reviewed all the reports in the literature up to 1934 and accepted 297 cases, including his own, as instances of true dissecting aneurysm of the aorta.

In the American literature since 1932 at least 65 cases have been reported. Hamburger and Ferris³ reported 6 cases in which the condition was discovered at autopsy, all 6 cases were observed within the short period of seven months, while in the preceding nine years only 10 cases had come to necropsy at the Cincinnati General Hospital. The incidence noted by other authors⁴ has been 1 case of dissecting aneurysm in 300 to 500 autopsies. The 4 cases described in this report were observed in the course of a year, during which time about 180 autopsies were performed and approximately 2,000 patients were treated in the hospital. Such a high incidence is undoubtedly fortuitous, but it is obvious that the dissecting type of aneurysm is not so uncommon and that the recognition of the condition is of practical as well as academic importance.

I report 4 cases of dissecting aneurysm, proved to be such at autopsy. Two of these will be described in some detail because the patients lived a considerable length of time (93 days and 14 months, respectively) after the onset of their illness. In one of these the diagnosis was made before

From the Cardiovascular Unit, Veterans' Administration, Washington, D C

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1 Osler, W, and McCrae, T. The Principles and Practice of Medicine, New York, D Appleton and Company, 1928

2 Shennan, T. Dissecting Aneurysms, Medical Research Council, Special Report Series, no 193, London, His Majesty's Stationery Office, 1934

3 Hamburger, M, Jr, and Ferris, E B, Jr. Dissecting Aneurysm, Am Heart J **16** 1 (July) 1938

4 (a) Glendy, R E, Castleman, B, and White P D. Dissecting Aneurysm of the Aorta, Am Heart J **13** 129, 1937. (b) Weiss S. Clinical Course of Dissecting Aneurysm of Aorta, M Clin North America **18** 1117, 1935

death (case 1) Of the patients, 3 were white and 1 was Negro Their ages ranged from 39 to 50 years, with an average of 44 years There was no evidence of syphilis in the history, serologic reactions or results of examination of any of these patients

REPORT OF CASES

CASE 1—A J M, a Negro aged 41, who had had no significant illnesses except pneumonia five years previously and who had been in good health until the presenting illness, was admitted to the hospital of the Veterans' Administration on Dec 14, 1936 He had never been told that his blood pressure was high, and nothing in his history suggested the presence of significant hypertension

He stated that after an evening meal, several days before his admission to the hospital, he suddenly had become nauseated and had vomited as he was going upstairs to his room He noticed some pain in the upper region of the abdomen at the time, and he took a dose of castor oil, which was promptly returned Not feeling any better, he went to a hospital, an enema was administered, and after about four hours' observation the physician allowed him to return home He continued to have nausea and abdominal discomfort, so his family physician was consulted, medication was prescribed, apparently for the relief of "ptomaine poisoning," but it was without effect After an attack of coughing an increase in the severity of his symptoms led him to apply for admission to this hospital

The chief complaints noted on admission were pain over the upper portion of the abdomen, especially on the right side, nausea, vomiting and "gas on the stomach" The first examiner was impressed principally by the abdominal symptoms and signs, although there was some question in his mind whether the complaints had an organic basis The abdomen seemed tender over the umbilicus, and the muscles on the right side were slightly rigid The temperature was 99.2 F, heart rate, 60, leukocyte count, 9,500 There were a few red blood cells in the urine The blood pressure was 150 systolic and 90 diastolic The heart was not enlarged, the rhythm was regular, and no murmurs were heard It was noted that the peripheral arteries were thickened to a marked degree for so young a man

During the following month in the hospital the patient did not feel well but did not appear seriously ill He continued to have inconstant pain in the epigastrium, extending around to the right lumbar region and down the spine, from the intercapsular region to the coccyx Drinking cold water increased the pain, and after eating he would become nauseated and regurgitate his food He did not sleep well at night, was constipated and passed only small quantities of urine The temperature during this period ranged from 100 to 101 F On the third day after admission there was leukocytosis (12,000 cells) The erythrocyte count on admission was 4,420,000, and the hemoglobin content was 14 Gm per hundred cubic centimeters, it dropped to 3,800,000, with a hemoglobin content of 10.5 Gm, in the course of a month The urine showed a specific gravity of 1.029, no red blood cells were noted after the first specimen After an intramuscular injection of 1 cc of phenolsulfonphthalein, he was able to void only one specimen at the end of an hour and none in the ensuing few hours The specimen voided did not contain enough dye to color the urine when alkalinized The chemical composition of the blood on the same day was within normal limits

Studies of the gallbladder showed no abnormalities Agglutination reactions were negative for typhoid, brucellosis and tularemia Intestinal tuberculosis was considered, but no acid-fast bacilli were discovered and the gastrointestinal roent-

genograms were normal. The first roentgenogram of the chest (fig 1) was taken two days after admission, the interpretation was that the heart was slightly enlarged, with widening of the supracardiac shadow. There was a definite projection of the first part of the aorta to the right, the arch was wide, and the

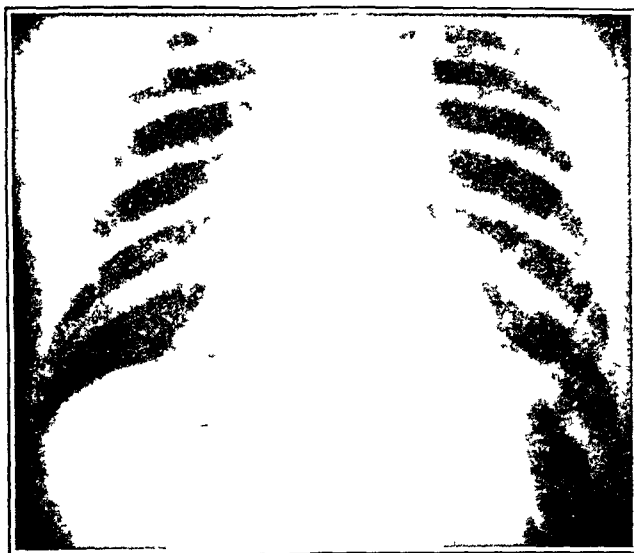


Fig 1 (case 1) —Roentgenogram taken (at a distance of 6 feet [1.8 meters]) on Dec 16, 1936, about a week after the onset of symptoms

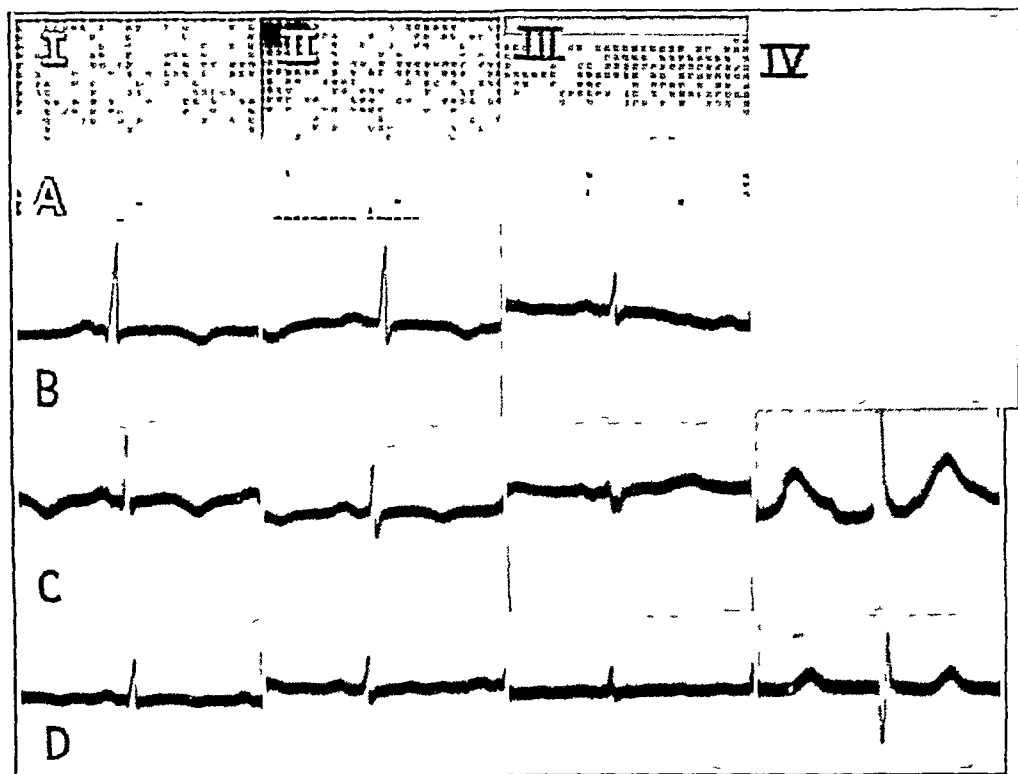


Fig 2 (case 1) —*A*, taken Jan 7, 1937, about a month after onset, *B*, Jan 18, *C*, Feb 24, *D*, March 2

knob was broad and rounded. The descending aorta was denser than usual and tended to fill the concavity above the left ventricle. The outline of the aorta appeared ragged, and the trachea was displaced to the right. An electrocardiogram

(fig 2 *A*) taken about three weeks after admission was essentially normal except for an occasional sinus premature contraction. On several occasions the rhythm of the heart suggested auricular fibrillation, but this was never confirmed by a tracing.

During the second month of his illness the patient felt fairly well although his temperature continued to be slightly elevated. He was able to go home on pass without any untoward effects until, toward the end of the month, the nausea and belching returned and there was pain in the left side of the chest and of the abdomen and in the back. A blood count at the end of the second month showed 3,180,000 red blood cells, with 9.8 Gm of hemoglobin per hundred cubic centimeters, and 17,950 white blood cells.

A second roentgenogram (fig 3 *A*) of the heart and aorta was made about this time. The cardiac shadow was greatly enlarged and the supracardiac shadow was wider, although the projection to the right noted in the first film was not observed. Instead, the right border of the aorta formed a wide arc, the more distal and outer portions of which were less dense. The aortic knob was less prominent,



Fig 3 (case 1) —*A*, roentgenogram taken (at a distance of 6 feet [1.8 meters]) on Feb 18, 1937. *B*, roentgenogram taken in recumbent position with use of Bucky diaphragm, March 5, 1937.

and the left supraventricular concavity was obliterated. The outline of the borders was still irregular.

Early in the third month of his illness the patient had a sudden attack of pulmonary edema, with marked dyspnea and shock. He did not complain of any particular pain. On examination the heart was appreciably enlarged, there were a gallop rhythm, a transient systolic murmur at the apex and accentuated second sounds at the base.

The patient had several such attacks over a period of forty-eight hours. Between the attacks he was fairly comfortable but occasionally complained of precordial pain. A blood pressure of 166 systolic and 108 diastolic was recorded during this period. The heart sounds did not seem abnormal, and no murmurs were heard.

A third roentgenogram of the heart and aorta (fig 3 *B*) was taken, using a Bucky diaphragm. The patient was in the recumbent position. This film was not comparable with the previous ones because of the change in position and technic, but it demonstrated the great widening of the aorta, particularly the

descending portion. An electrocardiogram (fig 2D) taken at this time showed inversion of the T waves in leads I and II, with an upright (minus) T wave in lead IV⁵ (original technic). The tracing did not suggest the acute changes of a coronary occlusion, although it was interpreted as showing evidence of myocardial damage.

At this time it was noted that arterial pulsation could not be felt in the popliteal, dorsalis pedis or posterior tibial arteries, although the femoral pulses were palpable. On the basis of this absence of pulsation, together with the changes in the roentgenograms of the heart and aorta, the absence of electrocardiographic changes typical of coronary occlusion and the absence of a drop in blood pressure a diagnosis of dissecting aneurysm of the aorta was made.

The patient continued to have attacks of pulmonary edema, with surprising recovery following each of the acute manifestations. Morphine and atropine, or morphine alone, were always administered and seemed to give relief. It was noticed that the percussion note posteriorly to the left of the spine from the fifth thoracic to the ninth thoracic vertebra was absolutely flat and that a loud, rough systolic murmur could be heard in this region and nowhere else. Also, the patient complained of pain around the left side of the thorax in a segmental distribution.

The patient manifested gradually increasing heart failure and was irrational, screaming out at times. The periodic attacks of dyspnea with pulmonary edema recurred, although the patient appeared comfortable immediately before death, which occurred just three months after admission and ninety-three days after the first symptom. Death was due not to external rupture of the aneurysm but to heart failure.

Postmortem Examination—The descending aorta presented a transverse tear of the intima across the entire circumference of the vessel, about 10 cm below the arch. Blood had accumulated within the split coats of the aorta throughout the thoracic and abdominal length of the aorta. About 5 cm above the bifurcation into the iliac arteries there was a second tear in the intima where a more saccular aneurysm, not connected with the previous one and containing an older, laminated clot, extended along the iliac arteries to Poupart's ligament. There was no evidence of erosion. The wall of the abdominal aorta was blackish and soft.

The pericardial sac contained about 200 cc of bloody fluid. The hemorrhage apparently originated in an adherent area at the reflection of the pericardium from the aorta. The heart weighed 460 Gm. The muscle was pale but had firm consistency, and on microscopic examination the muscle fibers were seen to be large. The coronary arteries showed only a few patches of atheromatous change.

The left pleural cavity contained several hundred cubic centimeters of serous transudate. The left lung was definitely contracted, due in part to the presence of fluid. The right pleural cavity had synechial adhesions but no clot. Both lungs were quite heavy and solid and were filled with frothy blood-tinged fluid, and in all lobes there were areas of pneumonic consolidation.

Comment—This patient presented a clinical picture which is less commonly described for dissecting aneurysm of the aorta. The absence of a history of previous hypertension does not necessarily indicate that the blood pressure had not been elevated, although it probably was never

5 The chest electrode was placed over the apex of the heart and connected to the left arm lead. The indifferent electrode was placed on the leg and connected to the left leg lead.

excessively high. There was no history of unusual exertion. Pain was not a prominent symptom, when present it was abdominal, and it did not become thoracic until late in the illness. Nausea and vomiting were the principal complaints, as will be noted in the succeeding histories, these symptoms were common to the other 2 patients from whom a history could be obtained. Low grade fever, leukocytosis, anemia and hematuria, often reported in patients with dissecting aneurysm, were present in this case. In retrospect, the rather sharp decline in the number of red cells and in the hemoglobin content during the course of the illness probably indicated loss of circulating blood into the aneurysm, it suggests that such a finding in a patient who survives for more than a few days may be of diagnostic significance.

The progressive changes in the electrocardiograms over the three month period are of some interest. The T waves in leads I to III were upright about three weeks after the onset of symptoms, and the ST segments in leads I and II were slightly elevated. A second tracing taken five weeks later showed inversion of the T waves in leads I and II and without any deviation in the ST interval. Five days later the T waves in leads I and II were again inverted and the T-wave in lead IV was upright (minus). In a tracing about two weeks before death the T waves in leads I and II were less deeply inverted and the T wave in lead III was flat, while the T wave in lead IV continued to be upright (minus). There was a progressive decrease in the voltage of the QRS complexes. These changes were not associated with any gross or microscopic evidence of infarction, and the coronary ostia and arteries were not involved. There was a small amount of fresh blood in the pericardium and a small area of chronic pericarditis with adhesions in the region of the aortic reflection of the pericardium, but it is questionable if the latter was responsible for the changes in the electrocardiogram, which resembled those observed with anterior infarction of the myocardium. Although no structural lesion in the heart was found to account for the abnormalities in the electrocardiogram, the fact remains that they developed after the onset of the dissecting aneurysm.

The roentgenograms also showed progressive changes during the course of the illness and, with the loss of pulsation in the arteries of the lower extremities, made the diagnosis of dissecting aneurysm tenable.

CASE 2—S. M., a white man aged 50, was first admitted to the hospital on Jan. 25, 1937. He stated that except for the usual childhood diseases he had been well until 1911, when he had acute nephritis with uremic coma. He was serving in the Marine Corps at that time and after treatment in the hospital was returned to duty. He was given a medical discharge in 1914, and the subsequent records to 1929 do not show a recorded blood pressure exceeding 130 systolic and 100 diastolic, even during acute attacks of disease.

He had gonorrhea in 1904 but denied any history of syphilis. After discharge from the service he was able to work as a police officer until January 1937, although he had noticed some shortness of breath and slight swelling of his ankles for about six months preceding his admission. Eight years before admission he had had an attack of "stomach trouble," diagnosed as a peptic ulcer and treated as such, with practically complete relief of symptoms.

One day in January 1937 he worked harder than usual, and the next day he had to stay in bed because of knifelike pains in his chest and dyspnea even at rest. The pain was not relieved until he received a hypodermic injection. He seemed to improve for a few days, then his symptoms recurred, with pain, nausea and emesis, extreme dyspnea and palpitation. He became unconscious and was brought to the hospital.

On admission he appeared to be dying, with Cheyne-Stokes breathing, auricular fibrillation (no electrocardiogram was taken) and a blood pressure of 60 systolic



Fig 4 (case 2) —Roentgenogram taken at bedside on Jan 27, 1937

and 40 diastolic. The following morning, however, the pain in his chest was relieved, the blood pressure was 148 systolic and 116 diastolic, and the heart was regular. The borders of the heart could not be satisfactorily determined, and the sounds were distant.

On admission the blood count showed 3,500,000 erythrocytes and 17,250 leukocytes, the hemoglobin was 11.2 Gm per hundred cubic centimeters. The leukocytosis gradually decreased. Three days after admission the nonprotein nitrogen of the blood was 46.1 mg per hundred cubic centimeters, the uric acid, 5.4 mg and the sugar, 78 mg. The urine varied in specific gravity from 1.017 to 1.025. Albumin was found in several specimens, a few white blood cells were always present, and there were red blood cells in 5 of 7 samples. A roentgenogram (fig 4) taken at the bedside did not reveal any areas of infiltration or consolidation in the lung fields, but the aorta was unusually wide to the right and the aortic knob was prominent and dense, with an irregular shadow extending below to the pulmonary artery. The heart did not appear enlarged.

An electrocardiogram (fig 5 *A*) taken two days after admission revealed a regular sinus rhythm, notched P waves in leads II and III, diphasic T waves in leads I to III and in lead IV a T wave which could not be distinguished from the other undulations in the tracing. Five days later an electrocardiogram (fig 5 *B*) showed definite inversion of all the T waves, deepest in leads II and III. There was no significant change in the ST intervals or in lead IV. These abnormalities were interpreted as evidence of myocardial damage but were not considered characteristic of acute coronary occlusion, although there had been changes in the configuration of the T waves in a period of five days.

The patient improved gradually, except that weakness persisted, and he was allowed to go home after two months of hospitalization, during which period his oral temperature had varied from 97 to 100 F.

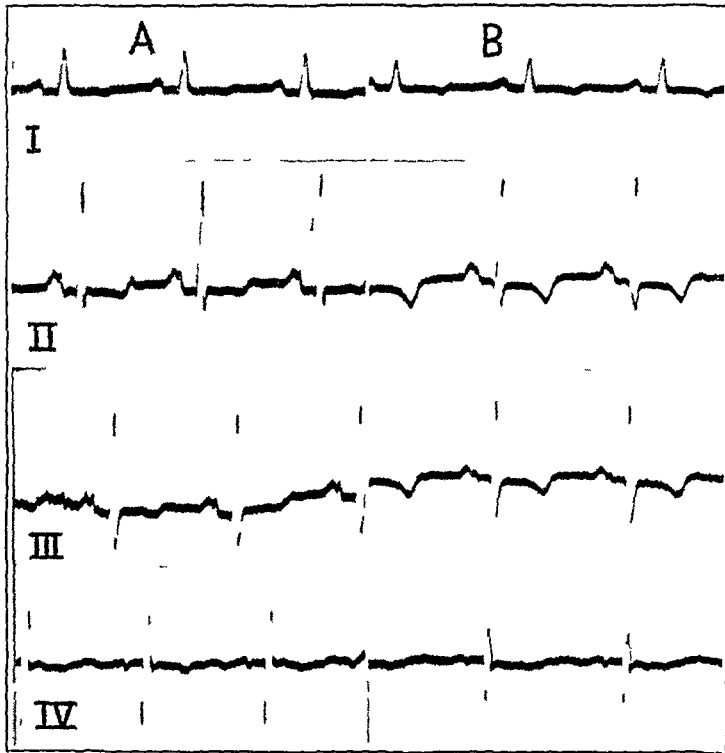


Fig 5 (case 2) —*A*, taken Jan 27, 1937, *B*, Feb 2

After his discharge from the hospital on March 26, 1937, the patient was more or less invalided because of dyspnea, precordial pain, weakness and palpitation. In late September 1937 he contracted a cold, with severe cough, fever, chills and recurring pains across the front of his chest. The patient was readmitted on Oct 4, 1937, for treatment of bronchopneumonia, he was obviously very ill, although his oral temperature was only 99.5 F. The breathing was labored but not exceptionally rapid, and he was coughing. The motion of the left side of the chest was markedly reduced, especially over the upper portion. The percussion note to the left above the level of the third interspace was flat, and the breath sounds were practically absent in this area. On the right the percussion note was hyperresonant except posteriorly between the spine and the scapula and anteriorly for 5 or 6 cm from the sternum, below the second rib. No rales were heard. It was observed that the veins of the left side of the neck and over the midportion of the left side of the chest were dilated.

A roentgenogram (fig 6 *A*) taken at the bedside at this time revealed a large shadow occupying the upper two thirds of the left side of the thorax. There was also a rounded opacity projecting from the cardiac and aortic shadow to the right between the second and fourth ribs anteriorly.

Two days later the patient was improved sufficiently for a roentgenogram to be taken in the erect position with the tube at 6 feet (183 cm). This plate (fig 6 *B*) presented essentially the same picture as the film taken at the bedside. The "arcuate excrescence" on the right border of the vascular area was more sharply defined, and in both roentgenograms this shadow was more definite and localized than in the plate taken nine months earlier (fig 5).

The patient's symptoms improved remarkably, and subsequent roentgenograms showed rather sharp demarcation of the shadow in the left upper region of the chest. It seemed most probable that the patient had a tumor of the lung, therefore material for a microscopic study was obtained by use of the bronchoscope, by puncture of the lung and by excision of a lymph node, but none of the specimens showed any abnormality. In spite of the negative results, the patient was given a course

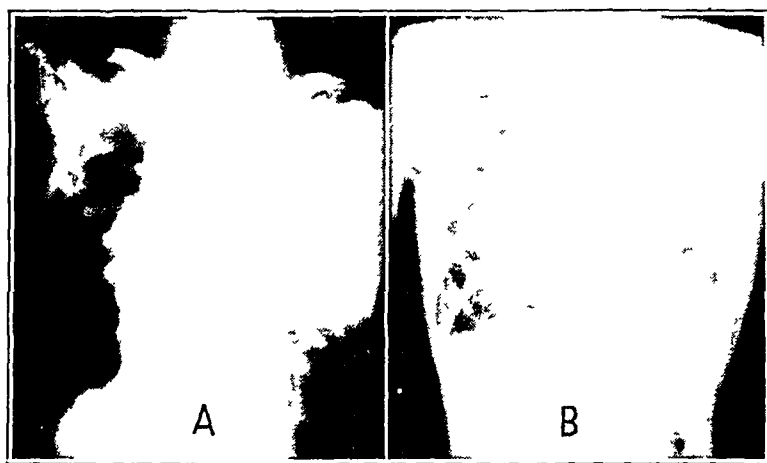


Fig 6 (case 2) —*A*, roentgenogram taken at bedside Oct 5, 1937, *B*, taken at a distance of 6 feet, October 7.

of high voltage roentgen therapy to the left lung. A roentgenogram taken about six weeks later (fig 7 *A*) showed some regression of the mass in the left upper region of the chest without change in the opacity to the right of the aorta. Another plate taken six weeks later (fig 7 *B*) showed further decrease in the size of the mass in the left upper region of the chest. The shadow on the right of the aorta was unchanged, and the aortic knob was obviously large and rounded, with a convex shadow filling the concavity between the knob and the left ventricle. This picture suggested a diagnosis of aneurysm, although the shadow in the left lung field was not explained.

The patient continued to improve and except for weakness felt quite well. He was nauseated at times, presumably because of the roentgen treatment, but at other times was able to eat a fair meal. About a week before his death he complained of some difficulty in swallowing liquids. Some edema of the ankles was also noted shortly before death, and, since no rales were heard in the lungs, the edema may have been largely due to his marked anemia rather than to congestive heart failure. In the last week of his life pain in the chest again developed,

and he was noticeably weaker. Death finally ensued after a profuse hemorrhage, in which blood gushed out from the oral cavity.

The laboratory examinations revealed a marked decrease in the number of red cells and in the amount of hemoglobin. There were 1,950,000 erythrocytes and 7 Gm of hemoglobin, as compared with 3,500,000 erythrocytes and 11.2 Gm of hemoglobin on the first admission. The urine contained albumin at the time of admission, and there were red blood cells in all of the specimens. The highest specific gravity was 1.022, the excretion of phenolsulfonphthalein was 15 per cent

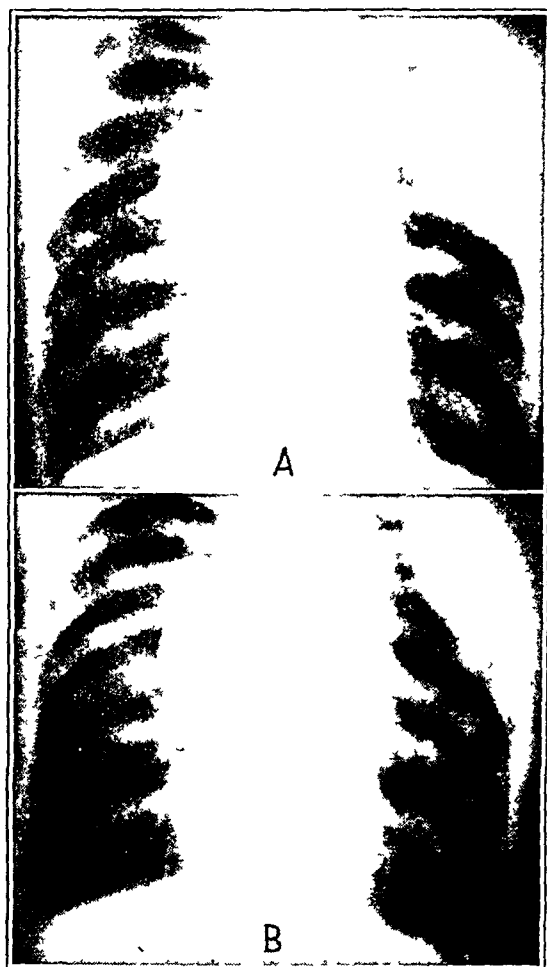


Fig 7 (case 2) —Roentgenograms taken at a distance of 6 feet, *A*, Dec 8, 1937, *B*, Jan 24, 1938

in two hours. The nonprotein nitrogen was 78.9 mg per hundred cubic centimeters, the creatine, 2.2 mg, the uric acid, 8.3 mg, the sugar 90 mg.

Postmortem Examination—The body was that of an emaciated white man of about 55 years (actual age, 50). Both pleural spaces contained about 500 cc of transudative fluid, which was not bloody, and on the upper outer aspect of the left pleura, near the posterior axillary line, there was a globular swelling. When cut into, the mass consisted of soft coagulated material with a yellowish muddy color, which proved to be necrotic blood without organization.

The pericardium contained a slight excess of clear, straw-colored fluid. The heart weighed 340 Gm, which was slightly above the normal limit for a man

who weighed 150 pounds (68 Kg) in health. The muscle grossly had good consistency, without fibrosis. The coronary arteries were patent and showed a moderate amount of intimal change, with considerable thickening of the wall, especially in the posterior artery. In several areas along the anterior descending artery there were small hemorrhages beneath the intima.

The aorta was inelastic, and the layers of the media were split from the beginning of the aorta to the arch, the fissure extending up into the great vessels of the neck. This space did not contain blood. At the posterior portion of the arch and along the thoracic aorta there appeared to be two sacs within the wall, one extending to the right, in close apposition to the esophagus and filled with a laminated clot, and the other projecting to the left and containing fresher blood. No sign of an intimal tear or of gross communication between the lumen of the aorta and the aneurysm was evident. The esophagus was constricted by the aneurysmal mass, and the mucosal surface in this area presented numerous punched-out ulcers which might have communicated with the aneurysm.

The origin of the blood in the periphery of the lung could not be definitely established, but presumably this blood had issued from a rupture through the adventitia and pleura. All of the bronchi, on both sides, were plugged with blood clots, probably from inspiration of blood during the terminal hemorrhages.

The kidneys were small, red and granular. The capsule of each was adherent, there were several small cysts in the parenchyma, and the cut surface showed a definitely reduced cortex, with white striae running out into it.

There was the scar of a healed ulcer on the anterior wall of the stomach in the prepyloric region.

Comment—In this case the history was more typical of the classic description of dissecting aneurysm in that the onset was characterized by severe pain following more strenuous exertion than usual. This, however, did not immediately precede the onset of symptoms. Nausea, emesis and, at times, dysphagia were also present. On several occasions there was severe circulatory shock, from which the patient recovered promptly to remain fairly comfortable for considerable periods of time. There were slight fever and leukocytosis at various times during the illness, and the progressive severe anemia was particularly significant. The urine regularly showed red cells, and there was retention of nitrogen in the blood, more marked immediately after acute attacks. The patient gave a history of acute renal disease twenty-six years before, and the renal insufficiency was probably due basically to chronic nephritis plus circulatory impairment subsequent to the development of the aneurysm. The records up to 1929 did not show elevation of the blood pressure, and the absence of marked cardiac hypertrophy would argue against prolonged hypertension.

Two electrocardiograms were taken during the patient's first stay in the hospital, more than a year before his death. In the first one the T waves in the leads I to III were diphasic, while the isoelectric line in lead IV was so irregular that a T wave could not be distinguished. The RS-T intervals were isoelectric. In a tracing taken five days later there was definite inversion of the T waves in leads I to III, with slight

depression of the RS-T intervals in leads II and III. The T wave in lead IV was isoelectric. The patient received only 2 cc of digifoline-Ciba, this was administered soon after his entrance to the hospital, and none was given subsequently. No electrocardiograms were taken during the second stay in the hospital. The autopsy did not reveal any gross areas of infarction, although a small ecchymotic area beneath the anterior coronary artery showed changes in the muscle indicative of necrosis with replacement by fibrous tissue. This, however, was a year after the electrocardiogram was taken, and the myocardial lesion was probably more recent. There may have been obstruction of the coronary ostia at some time, since the aorta in its first portion was dissected but did not contain blood when examined at autopsy.

The roentgenograms were particularly interesting because of the picture produced by the subpleural hemorrhage and the localized bulgings from the aorta, which led to the clinical diagnosis of pulmonary neoplasm. On the basis of the later roentgenograms, the presence of an aneurysm was suspected, and greater awareness as to the possibility of aortic dissection might have led to the diagnosis early in the course of the second hospitalization.

This patient lived a comparatively long time, perhaps because the aneurysm did not communicate, through an intimal tear, with the lumen of the aorta. This is a relatively uncommon occurrence and may be of importance in the consideration of the pathogenesis.

CASE 3—W. H. D., a white man of 48 years, an office manager, was admitted to this facility on March 18, 1937. The history was obtained from the patient's wife, who stated that he had been well until five years previously, when he began to suffer from faintness, vertigo and severe headaches. At that time his blood pressure was found to be 180 systolic and 120 diastolic. About one year before admission he had dyspnea, orthopnea, cough with blood-streaked sputum, and edema of the ankles, these symptoms had caused him to be bedridden for three months. Recovery from this episode of congestive failure was apparently quite good.

About seven days before admission to the hospital the patient experienced an attack of agonizing pain across the anterior part of the chest and in the back while lifting a heavy object at his home. The pain was severe for more than an hour, and a large dose of morphine was required to give any relief. Associated with the pain were nausea, emesis, dyspnea and cold, clammy sweating. The temperature was 99 F, and two days later, following a chill, it rose to 100 F. He had several attacks of pain of lesser degree after the first one, the following signs and symptoms were observed during one such attack: agonized facies, pallor, cold and perspiring skin, rapid and shallow breathing, clutching at the right posterior side of the chest with the left hand. The blood pressure was maintained in the region of 160 systolic and 120 diastolic, although it had been as high as 220 systolic and 150 diastolic before admission to the hospital. Death occurred on March 20, 1937, nine days after the onset of symptoms.

On admission the erythrocyte count was 3,750,000, the hemoglobin content, 13.5 Gm, the leukocyte count, 17,500. The urine was normal. An electrocardiogram

was not obtained. A roentgenogram (fig 8) taken at the bedside showed a wide supracardiac shadow, widening of the left border of the heart and an opacity in the right pulmonary field.

Postmortem Examination—The aorta was dilated but retained considerable elasticity, and the intimal surface was quite smooth up to the origin of the great vessels from the arch. Just beyond the opening of the left subclavian artery there was an irregular tear in the intima, extending somewhat transversely for about 4 cm. The layers of the aorta were dissected in both directions from this area for some distance, and there was a rupture through the external coats opposite the intimal tear. This opened into the posterior mediastinum, which contained large clots on both the left and the right side, with extension into the neck.

The heart weighed 600 Gm. The pericardium contained about 20 cc of serosanguinous fluid, and beneath the visceral pericardium, especially over the left

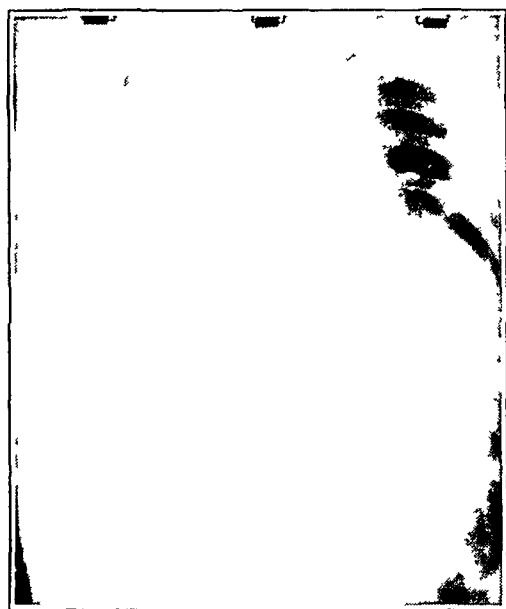


Fig 8 (case 3) —Roentgenogram taken at bedside March 18, 1937

auricular appendage, there was a hemorrhagic infiltration. The coronary arteries were not particularly sclerotic.

Both pleural cavities contained about 250 cc of serosanguinous fluid. The lungs were partially collapsed, dry and pale.

Comment—The history in this case fits the “classic” description of dissecting aneurysm. The patient was known to have had hypertension for several years, and a sudden attack of agonizing pain developed during strenuous exertion. The blood pressure tended to be maintained at a moderately high level except during shock associated with pain. The dissection was relatively limited. There were no consolidated or congested areas in the lungs to explain the shadow observed in the right lung field on the roentgenogram, this must have been associated with the contiguous hemorrhage into the mediastinum.

CASE 4—B. A., a white man of 39 years, was admitted to this facility on Sept 7, 1937, and died shortly after admission. Practically no history is available except

that he had complained of severe substernal pain before coming to the hospital, although his principal complaint when he was seen in the hospital was pain in the left leg

Postmortem Examination—The pericardium contained about 1,000 cc of blood, part of it clotted. The heart weighed 585 Gm, and the muscle had firm consistency.

The ascending aorta was dark colored because of the blood in the wall, which considerably reduced the lumen of the vessel. There was a tear through the intima about 2 cm in length, just above the sinuses of Valsalva, it communicated with the pericardial sac through a small opening proximal to the pericardial reflection on the aorta. There was a longer tear in the intima, distal to the first, extending longitudinally almost to the arch of the aorta. The outer coats of the ascending portion of the aorta were dissected. The wall of the descending and abdominal portions appeared intact, but at the bifurcation of the common iliac artery there was a small amount of clot in the wall without any intimal rupture.

Comment—Rupture into the pericardium is a fairly common terminal event in dissecting aneurysm.

COMMENT

Since the clinical manifestations of dissecting aneurysm have been so adequately reviewed in recent publications,⁶ only a few of the features of this condition will be emphasized.

A common description^{6a} of the onset of symptoms in dissecting aneurysm is that the patient "suddenly experiences an agonizing, tearing pain, usually in the anterior portion of the chest which feels as though something has been torn loose inside." Pain, indeed, is usually an outstanding symptom of dissecting aneurysm, and this diagnosis should be considered when pain is referred to the anterior part of the chest. It must be noted, however, that cases have been reported in which there was no complaint⁷ of pain referred to the chest. In some of these cases the patient was conscious of oppression or constriction in

6 (a) Blackford, L. M., and Smith, C. Coronary Thrombosis vs Dissecting Aneurysm in Differential Diagnosis, *J A M A* **109** 262 (July 24) 1937. (b) Claiborne, T. S., and Holler, E. D. Dissecting Aneurysm of the Aorta, *Am Heart J* **15** 358, 1938. (c) Boyd, L. J., and Werblow, S. C. Coarctation of the Aorta, Dissecting Aneurysm and Aneurysmal Dilatation of the left Vertebral Artery, *Ann Int Med* **11** 845, 1937. (d) McGeachy, T. E., and Paulin, J. E. Dissecting Aneurysm of Aorta, *J A M A* **108** 1690 (May 15) 1937. (e) Peery, T. M. Dissecting Aneurysm of the Aorta, *Am Heart J* **12** 650, 1936. (f) Osgood, E. F., Gourley, M. F., and Baker, R. Diagnosis of Dissecting Aneurysm of the Aorta, *Ann Int Med* **9** 1398, 1936. (g) Roesler, H., Gifford, U. G., and Betts, W. Dissecting Aneurysm of Aorta, *Am Heart J* **13** 426, 1937. (h) Wood, F. C., Pendergrass, E. P., and Ostrum, H. W. Dissecting Aneurysm of the Aorta, *Am J Roentgenol* **28** 437, 1932. (i) White, P. D., Badger, T. L., and Castleman, B. Dissecting Aortic Aneurysm Wrongly Diagnosed Coronary Thrombosis, *J A M A* **103** 1135 (Oct 13) 1934. (j) Shennan.² (k) Hamburger and Ferris.³ (l) Glendy and others.^{4a} (m) Weiss.^{4b}

7 Wood and others.^{6h} Hamburger and Ferris.³

the chest. As in coronary occlusion, the patient often does not remember or is incompetent to give details of his history, and the failure to elicit a definite history of pain does not necessarily preclude a diagnosis of dissecting aneurysm. One of our patients, who was semicomatose when admitted to the hospital, complained only of pain in his leg, although other informants stated that earlier he had located the pain in his chest.

Two other patients had pain in the chest at the onset, but in only 1 (case 3) did this symptom resemble that of the "classic" description, in the fourth patient (case 1) the pain was always referred to the abdomen until shortly before death. In this patient the descending and abdominal portions of the aorta were principally involved. Abdominal pain is quite common, it was the principal complaint in 30 of Shennan's 300 cases and in 15 of 50 recently reported. Pain may also be referred to the back, shoulders and other locations, in fact, the pain of dissecting aneurysm does not follow any definite pattern or have any particular location, and one is impressed by its tendency to migrate to different anatomic regions. Glendy, Castleman and White^{1a} pointed out that the radiation of the pain was rarely the same in any 2 of their patients.

In addition to these characteristics, a suggestive diagnostic feature is a sudden and dramatic onset of catastrophic symptoms, which may be surprisingly relieved, even without medication, if the patient survives the original attack. Symptoms tend to recur after intervals of relative comfort varying from hours to months, although in some cases the pain never recurs and the patient lives to die of some other cause.

The occurrence of fever, of gastrointestinal symptoms such as vomiting and dysphagia, of severe circulatory collapse with low blood pressure from which the patient may recover remarkably and of nervous symptoms such as paralysis and unconsciousness has already been noted. The laboratory examinations in our cases revealed leukocytosis and anemia, the latter was particularly significant in that it progressed during the course of the illness, presumably because of loss of circulating blood into the aneurysm and other tissues. In relation to such anemia, Osgood, Gourley and Baker^{6f} observed an increased icterus index, which they ascribed to destruction of hemoglobin. There was also evidence of renal insufficiency in 2 of our patients, manifested by azotemia in 1 and by albuminuria, hematuria and low dye excretion in both. In addition, 1 patient voided only small amounts of urine. The patient with azotemia had had renal disease, but his nitrogen retention greatly decreased following recovery from the acute phase of the dissecting aneurysm. It is probable that the renal blood flow was impaired in both cases by the reduction in the lumens of the tributaries at their orifices.

When pain in the chest is a presenting symptom, electrocardiographic evidence is often of great value in differentiating the possible causes. The data are not sufficient to establish what changes in the electrocardiogram, if any, are associated with dissecting aneurysm. In only 15 of 127 cases collected ^{6d} from the English literature up to 1937 were electrocardiograms reported. In some instances there were no deviations from the normal. White, Badger and Castleman ⁶ⁱ took three tracings within four days on a patient with dissecting aneurysm which did not vary in any essential detail and did not show any abnormality. Claiborne and Holley ^{6b} reported four tracings on a patient which showed only gradually decreasing voltage of the QRS complexes. The T wave in lead III was inverted in all tracings.

Others have reported electrocardiograms in cases of dissecting aneurysm which resemble those in cases of myocardial damage due to coronary occlusion. Glendy, Castleman and White ^{1a} showed a tracing with slight changes in the T waves in leads II and III suggestive of posterior occlusion. The right coronary ostium was involved in the aortic dissection.

McGeachy and Paullin ^{6d} described a series of six electrocardiograms on a patient with dissecting aneurysm in which T in lead I varied from upright to inverted, then became upright again and finally inverted. T in lead II showed increasing voltage as an upright wave and subsequently became diphasic. T in lead III was upright in all tracings, and in some it was of high voltage. In all of the electrocardiograms there was a tendency for the ST segment to be depressed in leads I and II and to be slightly elevated in lead III. The QRS complex in lead III tended to be monophasic downward, or diphasic with a deep Q wave. The changes observed in this series of electrocardiograms might be interpreted as evidence of acute myocardial damage which could not be localized to any particular aspect of the heart. Since the pericardium contained a large quantity of clotted blood, myocardial damage may have been responsible for the changes, although there was no mention of myocardial abnormalities other than hypertrophy.

Osgood, Gouley and Baker ^{6f} described two tracings from a patient with dissecting aneurysm, taken three and one-half months apart. In the first, the T waves in leads I and II were inverted, with slight depression of the ST segments in both leads. In the second tracing the depression of the ST segments in leads I and II was marked, with elevation of the ST segment in lead III. No infarction of the myocardium was found at autopsy. The ST segment in an electrocardiogram taken on a second patient with dissecting aneurysm also showed depression of the ST segment in leads I and II and elevation in lead III.

Hamburger and Ferris ³ described three electrocardiograms taken on a patient in which the T waves in leads II and III gradually became

inverted, with development of a deep Q wave in lead III. The ST segment became definitely elevated in leads II and III and slightly elevated in lead I, while the T wave in lead IV reversed its direction, apparently, from positive to negative. Except for the T wave in lead IV and the ST segment in lead I this would usually be considered evidence of damage to the posterior wall secondary to occlusion of the posterior artery. There was subepicardial hemorrhage surrounding the posterior artery about 1 cm below its origin, although it was not stated whether the lumen was decreased. There was no evidence of a myocardial infarct, and the authors did not think the pericardial hemorrhage was responsible for the electrocardiographic changes, since it must have been a terminal event.

The electrocardiographic abnormalities noted in my cases and in those reported by others indicate that the absence of changes in the electrocardiogram should help to eliminate coronary occlusion in the differential diagnosis of dissecting aneurysm, while the converse is not true. After the onset of dissecting aneurysm abnormalities may appear in the electrocardiogram which have no characteristic pattern but often may simulate that of acute coronary occlusion. Furthermore, there may be progressive changes in the various complexes, as in coronary occlusion, which do not indicate any particular pattern of localization. It is therefore not possible to exclude the diagnosis of dissecting aneurysm on the basis of noncharacteristic electrocardiographic abnormalities.

Roentgenography should offer considerable aid in the diagnosis of dissecting aneurysm, but unfortunately many patients are too ill to permit a satisfactory examination, and it is questionable whether a patient should be subjected to the exertion of having a teleoroentgenogram taken when a dissecting aneurysm is suspected. Occasionally, as in 2 of our cases, the condition of the patient is not so grave, and the additional information to be derived warrants taking roentgenograms. Wood, Pendergrass and Ostium^{6a} described the roentgenologic features in 7 cases. They directed attention to the deformity of the supracardiac shadow, which may be a mere widening or may be an arcuate excrescence arising from some part of the aorta. They think that an extension of the shadow along a cervical vessel is the most pathognomonic roentgenologic feature, although it is infrequently seen. Roesler, Gifford and Betts^{6b} pointed out that if an "aneurysm involves only a part of the circumference of the aortic vessel and has a predominantly lateral location with respect to the direction of projection, it will be visualized as an outer, lighter shadow." When possible, therefore, it is desirable to obtain oblique and lateral as well as sagittal projections. Since the majority of dissections occur in the ascending aorta, deformity of the shadow of this portion should be most common. It may be difficult to

differentiate the changes that occur in hypertension, aortitis or even mediastinal tumor from those of dissecting aneurysm, but displacement to the right of either the trachea (as in case 1) or the barium-filled esophagus offers suggestive evidence of gross enlargement of the arch. Irregularity in the outline of the shadow is often conspicuous and is also suggestive.

Since the dissection, if not immediately fatal, tends to be progressive, serial roentgenograms may clearly show changes which can be accounted for best by hemorrhage into the structure involved. In case 1 the changes in the roentgenogram led to the antemortem diagnosis, while in case 2 the interval between the examinations was so long that a rapidly growing neoplasm might have produced the abnormalities observed. The differentiation was further complicated in this instance by the large opacity in the left upper part of the chest. Fluid has been noted frequently in the left pleural cavity and occasionally in the right, but it is usually seen at the base of the cavity. In one of the cases reported by Wood, Pendergrass and Ostrum⁶ there was an extension of the shadow of the aortic knob which partially obscured the left upper portion of the chest, and they mention that in 2 of their cases nonfatal rupture of the aneurysm into the mediastinum occurred. It is necessary, therefore, to consider the possibility of hemorrhage into the lung, pleura and mediastinum from a dissecting aneurysm in the differentiation of shadows in the lung fields, especially when there is deformity of the supracaeliac shadow.

The causes of dissecting aneurysm deserve some comment. The conception that the dissection is always or even usually dependent on a primary rupture of the intima followed by escape of blood from the lumen into the wall of the vessel is not acceptable. One of our patients presented a massive dissection of the aorta without any apparent break in the intima, and the fourth showed a small isolated hemorrhage with dissection without intimal rupture. Intimal tears were not observed in 2 of the cases observed by Hamburger and Ferris,³ and Winternitz⁸ made the statement that "there can be no doubt that the dissecting aneurysm arises from hemorrhage within the vessel wall, it does not have its origin from a tear of the innermost surface." Indeed intimal tears and acute rupture of all coats may occur without dissection. Shennan questioned whether the pressure in the vasa vasorum is high enough to act as a dissecting force, in commenting on the dissecting aortitis described by Babes and Mironescu, and assumed that "the local splitting is favored by degenerative changes in the media, which must accompany and are really dependent on the vascular alterations." Peery⁹

8 Winternitz, M. C., Thomas, R. M., and LeCompte, P. M. Studies in the Pathology of Vascular Disease, *Am Heart J* **14** 480, 1937.

Shennan² and others have described degenerative and inflammatory changes in the media of the aorta. Those which Shennan observed were seldom localized, but usually widespread, he concluded that degeneration of the media, due to toxins in most cases, was "the most important determining factor in the causation of dissecting aneurysm." Peery stated that it was a general belief that disease of the aortic wall, usually of an atherosclerotic nature, was the most important factor predisposing to dissection. Since dissection occurs in arteries with comparatively little intimal change—without intimal rupture and usually with no changes closely related anatomically to those of atheroma—it seems more probable that the primary disease involves the inner coats rather than the intima. Whether this damage is due to toxins or to vascular changes cannot be definitely established at present. Certainly hemorrhage into the walls of blood vessels from the vasa vasorum is not uncommon and may be extensive enough to fill an aneurysm of considerable size. Both the intimal rupture usually observed and the external rupture may be comparatively late events.

SUMMARY

Four cases of dissecting aneurysm, with postmortem examinations, are reported. In 1 case the diagnosis was made before death.

Two cases were observed for periods of three months and fourteen months respectively. The changes present in the electrocardiograms and roentgenograms in these cases are discussed.

The absence of the typical pain of the syndrome was conspicuous in 3 cases, although in all cases severe symptoms developed rather abruptly.

There was severe progressive anemia in 2 cases.

The absence of intimal rupture in 1 case suggests that intramural changes may be important in the causation of dissecting aneurysms.

HYPERTHYROIDISM AND DIABETES

JAMES F REGAN, M D

Fellow in Surgery, the Mayo Foundation

AND

RUSSELL M WILDER, M D, P H D

ROCHESTER, MINN

In 1926 one of us (Wilder¹) reported a study of 38 cases of hyperthyroidism and diabetes. The patients were observed during the period from Jan 1, 1923, to Dec 31, 1925, inclusive. The present study is that of a series of patients seen during a similar period, from Jan 1, 1935, to Dec 31, 1937, inclusive. The patients in both series were divided into two groups—those with exophthalmic goiter, and those with adenomatous goiter and hyperthyroidism, according to Plummer's classification². In order to exclude any but true diabetic patients we used Joslin's standard for diagnosis of diabetes in hyperthyroidism, which, as stated in his book, is a blood sugar content of 0.15 per cent during fasting or of 0.20 per cent or more after meals, in addition to glycosuria.

Table 1 shows the frequency of occurrence of diabetes combined with hyperthyroidism. A comparison is made with the figures obtained in 1926. Data for the frequency of occurrence of diabetes with adenomatous goiter without hyperthyroidism have been included in the later series.

During the interval of twelve years between reports the incidence of frank diabetes as a complication of hyperthyroidism has increased from 1.1 per cent to 3.2 per cent. As in the first report, its occurrence is more frequent in adenomatous goiter with hyperthyroidism (5.6 per cent) than in exophthalmic goiter (1.7 per cent). The fact that exophthalmic goiter occurs in a younger age group may partially explain this discrepancy. The average age of the patients with exophthalmic goiter and diabetes was 50.3 years, and that of patients with adenomatous goiter with hyperthyroidism and diabetes was 56.6 years. Another explanation

From the Division of Medicine, the Mayo Clinic (Dr Wilder)

Read at the meeting of the American Association for Study of Goiter, Rochester, Minn., April 17, 1940.

1 Wilder, R. M. Hyperthyroidism, Myxedema and Diabetes, *Arch Int Med* **38** 736-760 (Dec) 1926.

2 Boothby, W. M., and Plummer, W. A. Diseases of the Thyroid Gland, in Christian, H. A. *Oxford Medicine*, New York, Oxford University Press, 1936, vol. 3, pt. 2, pp. 839-964 (43).

is to be found in the duration of the hyperthyroidism in the two groups. Patients with exophthalmic goiter seek medical attention earlier, as a rule, than do those with the more insidious form of hyperthyroidism accompanying adenomatous goiter. Therefore, more opportunity for precipitating diabetes is given by adenomatous goiter with hyperthyroidism.

An attempt was made to ascertain the priority in appearance of symptoms of diabetes or hyperthyroidism. Owing to the uncertain onset of each disease and to the fact that certain symptoms, notably bulimia, loss of weight and weakness, are common to the two conditions, satisfactory conclusions frequently could not be reached. That the hyperthyroidism preceded in many cases is, however, quite clear.

TABLE 1—*Incidence of Combined Diabetes and Hyperthyroidism**
(Jan 1, 1935 to Dec 31, 1937, Inclusive)

Disease	Cases		Complicating Disease	1923-25		1935-37	
	1923-25	1935-37		Cases	Per Cent of Total	Cases	Per Cent of Total
Adenomatous goiter with hyperthyroidism	1,131	750	Diabetes	23	2.0	42	5.6
Exophthalmic goiter	2,340	1,132	Diabetes	15	0.6	19	1.7
Adenomatous goiter with hyperthyroidism plus exophthalmic goiter—total	3,471	1,882	Diabetes	38	1.1	61	3.2
Adenomatous goiter without hyperthyroidism		2,277	Diabetes			38	1.67

* In these counts, patients entering because of recurrence of hyperthyroidism within the three year period are counted more than once. The number of these, however, is too small to affect the significance of this table.

In the series of 1,132 patients with exophthalmic goiter seen at the clinic from 1935 to 1937, inclusive, there were 19 who had diabetes. Eleven were women, and 8 were men. Six did not require insulin for control of diabetes. The others required from 15 to 180 units per day, the average was 50 units per day. The basal metabolic rate varied from +9 to +97 per cent, the average was +38 per cent. Thirteen patients were operated on. Within the first few weeks after operation their basal metabolic rates varied from -14 to +34 per cent (average +8 per cent). The insulin requirement of 5 patients increased immediately after operation but, with that of the rest of the patients on whom operation was performed, it fell below or to the preoperative maintenance level within fourteen days. Ten of the patients who were operated on required much less insulin than they had taken on admission to the clinic. In 2 patients acidosis developed immediately after operation, but this was easily controlled. Seven of the 19 patients in this group had recurrent exophthalmic goiters. One patient died in

coma two days after dismissal from the clinic, thyroidectomy had been advised but was refused

In the series of 750 patients who had adenomatous goiter with hyperthyroidism, 42 also had diabetes. The female sex predominated, as in the previous group, but to a much greater degree—34 of 42 as compared with 11 of 19.

The basal metabolic rate of the 42 patients studied in this group ranged from +3 to +57 per cent, the average was +27 per cent. Twenty-nine of these patients were operated on. Within the first few weeks after operation their basal metabolic rates varied from -8 to +26, average +10 per cent. The doses of insulin given preoperatively ranged from 10 to 140 units per day. The average dose was 50 units per day. The insulin requirements of 12 patients increased during the first few postoperative days. In all but 5 of the patients who were operated on the requirement fell below the preoperative maintenance level within two weeks. In 4 patients acidosis developed postoperatively. This was readily controlled. One patient died on the sixth postoperative day. Death in this instance was due to cerebral arteriosclerosis and infarct of the brain.

Fitz,³ in 1921, stated that nontoxic thyroid disease does not affect diabetes. In his series the patients with nontoxic goiter who were operated on showed no improvement of the diabetes. Wilder in 1926 came to the same conclusion. In the present series there were 38 patients with adenomatous goiter and diabetes but no clinically evident hyperthyroidism. Their average age was 57.4 years. Women predominated as in the other groups, the ratio being 22 to 16. The basal metabolic rates ranged from -16 to +14 per cent, the average was +2 per cent. Sixteen patients required insulin for control of the diabetes. The remainder were treated with dietary restrictions. The doses of insulin ranged from 15 to 115 units per day, the average being 42 units. Thyroidectomy was performed on 7 of these patients. Their basal metabolic rates preoperatively ranged from +1 to +13 per cent, the average was +8 per cent. Four required insulin preoperatively in doses of 11 to 50 units daily. Six required insulin for several days postoperatively in doses of 15 to 120 units daily. One patient who had not taken insulin before operation required 70 units on the fourth postoperative day. Later her diabetes was readily controlled without insulin.

The following case report is an example of severe exacerbation of diabetes that at times may be observed postoperatively in patients with adenomatous goiters associated with normal basal metabolic rates and

3 Fitz, R. The Relation of Hyperthyroidism to Diabetes Mellitus, *Arch Int Med* 27:305-314 (March) 1921.

no clinical evidence of hyperthyroidism. The observation is believed to have important clinical significance and heretofore has received no comment in the literature.

REPORT OF A CASE

A man 54 years of age presented himself for examination with no other complaint than fatigue of about two years' duration. Polyuria and polydipsia had been noted for several weeks, but the urine had not been examined for sugar. The maximal body weight of 250 pounds (113.4 Kg) had been reached eleven years previously, and, partly by dieting, had been reduced to 205 pounds (93 Kg). In the last year an additional 9 pounds (4.1 Kg) had been lost.

Examination showed a man weighing 196 pounds (88.9 Kg) with a blood pressure of 154 systolic and 100 diastolic and a pulse rate of 96 per minute. The thyroid was enlarged and was very hard. The condition of the thyroid had been noted in a previous examination at the clinic in 1927, but operation had not then been advised. Examination of the urine revealed the presence of a trace of reducing substance, and a determination of the blood sugar during fasting revealed 226 mg per hundred cubic centimeters. The basal metabolic rate was $+4$ (two tests). The clinical diagnosis was adenomatous goiter without hyperthyroidism.

A diet containing 238 Gm of carbohydrate was prescribed. Also, compound solution of iodine was given. It was found necessary to use 25 units of insulin daily to control glycosuria. After ten days, the fasting blood sugar being 161 mg per hundred cubic centimeters, operation was performed. Intense glycosuria followed and for the next seven days was controlled with difficulty. The daily doses of insulin were 95, 115, 60, 70, 55, 55 and 80 units, and the amounts of sugar in the urine for the first four of these days were 17, 29, 12 and 30 Gm respectively. All specimens also contained acetone and diacetic acid. Otherwise, the degree of postoperative reaction seemed not abnormal. The maximal temperature reached, on the third day, was 102 F, and after the fourth day the patient was free from fever. Subsequently the doses of insulin could be rapidly decreased, so that by the end of the second week 12 units of protamine zinc insulin in one dose daily was sufficient to prevent glycosuria. Although the postoperative behavior of this patient was cause for some apprehension, the ultimate result was entirely satisfactory. The report of the pathologist on the tissue removed at operation was as follows: weight 160 Gm, multiple, hyaline, hemorrhagic, cystic fibrous, calcareous, degenerating, fetal and colloid adenomas in a colloid thyroid.

FOLLOW UP OF CASES IN 1926 STUDY

A complete follow-up study was made of all the 38 cases of hyperthyroidism with diabetes reported by one of us (Wilder) in 1926. In 12 of the 15 cases of exophthalmic goiter and diabetes operations were done. In 7 of these the patients have survived thyroidectomy an average of thirteen and eight-tenths years. The average duration of life in the five cases in which death has occurred was eight and one-tenth years after thyroidectomy. Death in these cases was attributed to coma, diabetes, lobal pneumonia, coronary thrombosis and heat stroke. Two of the 3 patients who were not operated on died of coma, and the other died with diabetes within a few months after dismissal.

Twenty-one of the 23 patients with adenomatous goiter with hyperthyroidism and diabetes were operated on. Five of these now are living, having survived thyroidectomy an average of thirteen and six-tenths years. The average duration of life in the 16 cases in which death has occurred was seven and four-tenths years after thyroidectomy. The causes of death were heart disease, 7, pneumonia, 3 and coma, gangrene (right leg), carbuncle on the back of the neck, cerebral hemorrhage, recurrent carcinoma and acute cholecystitis, 1 each. One of the 2 patients not operated on died of cardiac decompensation three months after admission. The other died ten years later of cardiac and renal disease.

Joslin has reported the average duration of life, subsequent to the onset of diabetes, among deceased ex-patients of all ages in the early Banting (1922-1926), middle Banting (1926-1930) and later Banting (1930-1935) periods as seven and six-tenths, eight and four-tenths and eleven years respectively. When all the patients in Wilder's series of 1926 are considered, except the 5 who did not have thyroidectomy the average duration of life subsequent to the onset of diabetes was twelve and four-tenths years. When only those patients who now are dead are considered, again excluding the 5 who did not have thyroidectomy, the average duration of life subsequent to the onset of diabetes was ten and eight-tenths years. The numbers in both of these groups are too small to justify comparison with the large groups (514, 897 and 981 cases respectively) of Joslin's deceased patients with diabetes studied by the statistical bureau of the Metropolitan Life Insurance Company. They, nevertheless, support the assumption that patients with hyperthyroidism and diabetes who receive satisfactory surgical treatment for their hyperthyroidism do as well as patients with diabetes free of this complication. The fact that 4 of the 5 who were not operated on died within a few months of the time they were dismissed from the clinic emphasizes the importance of performing thyroidectomy in cases of associated hyperthyroidism and diabetes.

COMMENT

Thyroxine has been shown to increase both anabolic and catabolic processes within the cells, the effects depending on the amount used. The metabolism of fats, carbohydrates and proteins is affected, and the distribution of minerals and water is also modified. Kendall⁴ stated

These observations suggest that the changes which are associated with a marked increase in the B M R are but an exaggeration of the normal metabolic activity of the cell without distortion and with utilization of metabolites according to their

⁴ Kendall, E. C. The Influence of Some of the Ductless Glands on Metabolic Processes, *Endocrinology* **24** 798-805 (June) 1939

availabilities. The only change is in the capacity for production of energy. However, when another hormone, as insulin or cortin, is deficient then the symptoms caused by the deficiency are aggravated and the fault in the metabolic processes becomes more marked when thyroxine is administered even in relatively small amounts.

The clinical observations recounted fully confirm this opinion. With the onset of hyperthyroidism previously existent diabetes is intensified, and with correction of the hyperthyroid state by thyroidectomy the intensity of the accompanying diabetes is diminished.

Further study reveals that the decreased incidence of hyperthyroidism among diabetic patients was coincident with the decline in the number of all hyperthyroid patients coming to the clinic.

The incidence of diabetes in patients with exophthalmic goiter for the period 1935 to 1937, inclusive, was 1.7 per cent. This is the same as the incidence of diabetes among all new patients registering at the clinic during the same period. With regard to the incidence of diabetes in patients with adenomatous goiter and hyperthyroidism there is a different story. During the same period 5.6 per cent of all patients with adenomatous goiter and hyperthyroidism had diabetes. This percentage was over three times that for the incidence of diabetes among new patients registering at the clinic. As shown in table 1, Wilder reported an incidence of 2.0 per cent in 1926, which at that time was nearly twice the incidence of diabetes among new patients. Joslin and Lahey⁵ reported 28 instances of diabetes among 655 patients with secondary hyperthyroidism, an incidence of 4.3 per cent. That age is not the factor explaining this high incidence of diabetes in the patients with adenomatous goiter and hyperthyroidism (whose average age was 56.6 years) is shown by the occurrence of diabetes in only 1.67 per cent of the patients with adenomatous goiter without hyperthyroidism (whose average age was 57.4 years).

The incidence of diabetes among patients with adenomatous goiter without hyperthyroidism was, as just stated, 1.67 per cent. This was about the same as among new patients registering at the clinic, 1.7 per cent. Surgeons must handle such patients with the same care that is indicated when the goiter is toxic. Occasionally there is marked increase in the severity of the diabetes, usually beginning within the first twenty-four hours after thyroidectomy, and lasting two to five days. The most logical explanation of the phenomenon is the mechanical liberation of large amounts of thyroid hormone as a result of operation, the absorption of the hormone leading to a temporary increase in the rate of metabolism and an accompanying requirement for more insulin.

⁵ Joslin, E. P., and Lahey, F. H. Diabetes and Hyperthyroidism, *Am J M Sc* **176** 1-22 (July) 1928.

Thyroidectomy was performed on 42 of the 61 patients with hyperthyroidism and diabetes. There was 1 fatality, which occurred in the case of a woman aged 73 who died on the sixth postoperative day. As stated before, postmortem examination revealed cerebral arteriosclerosis and infarct of the brain.

SUMMARY

Sixty-one cases of frank diabetes combined with states of hyperthyroidism were studied. Diabetes occurred with a frequency of 32 per cent in all cases of hyperthyroidism. The incidence in cases of exophthalmic goiter was 17 per cent, in those of adenomatous goiter with hyperthyroidism it was 56 per cent. In the latter group the evidence clearly indicates that hyperthyroidism was a factor of etiologic significance in the precipitation of the diabetes.

Thirty-eight patients with diabetes and adenomatous goiter without clinical evidence of hyperthyroidism were studied. Thyroidectomy was performed on 7 of these patients. Six required large postoperative doses of insulin, and difficulty was encountered in the control of their diabetes for the first three to five postoperative days. The case of 1 such patient is reported in detail.

A follow-up study was made of Wilder's 38 patients who had hyperthyroidism with diabetes. When those who did not have thyroidectomy were excluded, the average duration of life after the onset of diabetes was found to be 12.4 years. The data obtained support the assumption that patients with hyperthyroidism and diabetes who receive satisfactory surgical treatment for their hyperthyroidism do as well as patients with diabetes free of this complication, whereas those who are not relieved by operation fare badly.

CLINICAL MANIFESTATIONS OF PAROXYSMAL HYPERTENSION ASSOCIATED WITH PHEO- CHROMOCYTOMA OF ADRENAL

REPORT OF A PROVED AND OF A DOUBTFUL CASE

E F VAN EPPS, M D

O R HYNDMAN, M D

AND

JAMES A GREENE, M D

IOWA CITY

Paroxysmal hypertension due to an adrenal medullary tumor may progress so far as to cause death from irreparable vascular damage, or death may ensue from other causes. The disease can be diagnosed in its early stages and eradicated by surgical intervention. There are excellent reviews of the literature by Belt and Powell,¹ Wells and Boman,² Nuzum and Walton,³ Edward,⁴ Lazarus and Eisenberg⁵ and Collier, Field and Durant.⁶ Although there have been many valuable case reports, including those of the authors just mentioned as well as those of Beer, King and Prinzmetal,⁷ Evans,⁸ Holst,⁹ Binger and Craig,¹⁰

From the Departments of Internal Medicine and Surgery of the State University of Iowa College of Medicine

1 Belt, A E, and Powell, T O Chromaffin Cell Tumors of Suprarenal Medulla. Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla, Surg, Gynec & Obst **59** 9-24 (July) 1934

2 Wells, A H, and Boman, P G The Clinical and Pathologic Identity of Pheochromocytoma, J A M A **109** 1176-1180 (Oct 9) 1937

3 Nuzum, F R, and Walton, J W Paroxysmal and Persistent Hypertension in Association with Lesions of the Adrenal Glands, Am Heart J **16** 643-662 (Dec) 1938

4 Edward, D G Pheochromocytomata and Hypertension, J Path & Bact **45** 391-403 (Sept) 1937

5 Lazarus, J A, and Eisenberg, A A Tumors of Adrenal Gland. Report of Two Cases of Paraganglioma of Adrenal Gland, J Urol **27** 1-26 (Jan) 1932

6 Collier, F A, Field, H J, and Durant, T M Chromaffin Cell Tumor Causing Paroxysmal Hypertension Relieved by Operation, Arch Surg **28** 1136-1148 (June) 1934

7 Beer, E, King, F H, and Prinzmetal, M Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, Ann Surg **106** 85-91 (July) 1937

8 Evans, V L Suprarenal Tumor with Paroxysmal Hypertension, J Lab & Clin Med **22** 1117-1120 (Aug) 1937

(Footnotes continued on next page)

Brunschwig, Humphreys and Roome,¹¹ Kremer,¹² Kelly, Piper Wilder and Walters,¹³ MacKenzie and McEachern,¹⁴ and Palmer and Castleman,¹⁵ together with those in the foreign literature, the clinical features of the disease have not been duly stressed. It is for this reason that we are reporting 2 cases of paroxysmal hypertension and emphasizing the manifestations.

REPORT OF CASES

CASE 1—A white single man aged 27 was admitted to the University Hospitals on Sept 10, 1938, because of attacks of swelling of the neck of three years' duration. The attacks were more prominent during the fall and winter, but they were induced also in the summer by working in the field. The patient thought that the wearing of suspenders played a role in their induction. The duration of the attacks varied from only a few hours to as long as a day. The usual accompanying manifestations were a sense of swelling of the neck, a forceful heartbeat which was rarely rapid, throbbing occipital headache, nervousness, sweating, weakness, easily induced fatigue, polyuria and constipation. Occasionally nausea and vomiting occurred, and on only one occasion was shortness of breath noted. Precordial and epigastric distress, cyanosis, air hunger, tingling of the extremities, changes in color of the extremities or nose, vertigo, tinnitus, epiphora, sialorrhea and diarrhea did not occur.

The objective manifestations revealed by examination of the patient on admission were as follows. The patient was a tall, thin man with acromegalic facies. He had several yellowish neuromas of the conjunctiva of each lid, false teeth, a slightly palpable thyroid gland, forceful carotid pulsations with leathery arterial walls, an upper dorsal kyphosis, long, slender fingers and hypere extensibility of the fingers and knees. The heart was of normal size and had an accessible left ventricle, a constant systolic murmur was observed at the apex and the arterial pressure was variable, ranging from 98 to 260 systolic and from 56 to 150 diastolic.

Slight albuminuria was observed. The hemoglobin content of the blood was 13 Gm per hundred cubic centimeters, and the blood count was erythrocytes 4,420,000 and leukocytes 8,000. The Wassermann reactions of the blood and the spinal fluid were negative. The basal oxygen consumption was 14 per cent below

9 Holst, E J. Three Cases of Chromaffin Cell Tumors of the Supra renal Glands, *Acta med Scandinav* **94** 510-526, 1938.

10 Binger, M W, and Craig, W M. An Atypical Case of Hypertension with a Tumor of the Adrenal Gland, *Proc Staff Meet, Mayo Clin* **13** 17-20 (Jan 12) 1938.

11 Brunschwig, A, Humphreys, E, and Roome, N. Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, *Surgery* **4** 361-370 (Sept) 1938.

12 Kremer, D N. Medullary Tumor of Adrenal Gland, with Hypertension and Juvenile Arteriosclerosis, *Arch Int Med* **57** 999-1002 (May) 1936.

13 Kelly, H M, Piper, M C, Wilder, R M, and Walters, W. Case of Paroxysmal Hypertension with Paraganglioma of Right Suprarenal Gland, *Proc Staff Meet, Mayo Clin* **11** 67-70 (Jan 29) 1936.

14 MacKenzie, D W, and McEachern, D. Tumor of Medulla of Adrenal, *J Urol* **40** 467-476 (Oct) 1938.

15 Palmer, R S, and Castleman, B. Paraganglioma (Chromaffinoma, Pheochromocytoma) of the Adrenal Gland Simulating Malignant Hypertension, *New England J Med* **219** 793-796 (Nov 17) 1938.

normal Intrathecal pressures were normal Tests of the cerebrospinal fluid gave normal readings

Subsequent Course and Findings—The paroxysms occurred almost daily, giving an excellent opportunity for the study of the various manifestations No alterations were produced in the electrocardiogram, but glycosuria, albuminuria, cylindruria and hyperglycemia, with a sugar content as high as 273 mg per hundred cubic centimeters, developed during a paroxysm The blood sugar levels at comparable times of the day, without an attack, were 110 to 118 mg per hundred cubic centimeters Between attacks the renal urea clearance was 90 per cent of normal, but it was reduced to 53 per cent of normal during an attack Determinations of the chemical constituents of the blood revealed urea nitrogen 12.6 mg, creatinine 1.0 mg, serum proteins 6.81 Gm, calcium 10.2 mg and phosphorus 4.7 mg per hundred cubic centimeters The sella turcica was of normal size A biopsy of the pectoralis major muscle showed normal arteries and arterioles The cold pressor test failed to produce an attack on two occasions

Localization of the tumor was difficult Intravenous and retrograde pyelograms, soft tissue roentgenograms of the adrenal regions and perirenal insufflation of air gave no added information

The right adrenal region was explored through a posterior approach with the patient under ether anesthesia A tumor which measured 4 by 6 cm was found adherent to the adrenal gland and necessitated removal of the gland also Manipulation of the tumor in situ produced an increase of both systolic and diastolic arterial pressures The removal of the tumor, however, resulted in a rapid fall in arterial pressures, which was finally checked at 60 systolic and 20 diastolic by the subcutaneous administration of epinephrine The arterial pressures rose gradually to 80 systolic and 50 diastolic by evening, and to 110 systolic and 80 diastolic the following morning, where they remained until the patient's discharge from the hospital three months later The postoperative course was stormy for the first two days and was further marred by the development of pneumonia, complicated by empyema In addition to the usual postoperative therapy, large amounts of sodium chloride and 10 cc of adrenal cortex extract were administered daily for two weeks Microscopic examination of the tumor revealed that it was a pheochromocytoma

The possibility that Addison's disease might develop because the right adrenal gland had been removed and the condition of the left adrenal gland was unknown caused us to carry out the procedure recommended by Cutler, Power and Wilder¹⁶

The results were within normal limits, and the patient manifested no evidence of adrenal cortical insufficiency three months after the operation

CASE 2—A white married woman 34 years of age was admitted to the University Hospitals on Nov 1, 1938, because of inability to walk, high blood pressure and heart trouble She had not been well for twenty years There had been many functional complaints, such as severe matutinal pressure headaches, occasional nausea and vomiting and diminution of vision These symptoms had not increased, but on Aug 14, 1938, the patient suddenly became unconscious for the first time and remained in this state for about one hour There were no convulsions On regaining consciousness she noted a stabbing pain which appeared in the upper part of the left arm and in the left shoulder and radiated to the precordium This pain persisted until admission Usually it was a dull ache, but two or three times a week it was aggravated, being on those occasions acute, knifelike and stabbing At such

16 Cutler, H, Power, M H, and Wilder, R M Concentration of Chloride, Sodium and Potassium in Urine and Blood Their Diagnostic Significance in Adrenal Insufficiency, J A M A **111** 117-122 (July 9) 1938

times the face and lips became pale and the breath short and occasionally nausea and vomiting occurred. Abasia had caused the patient to remain in bed since the onset of the symptoms. The previous symptoms became aggravated, and her physician stated that she had high blood pressure and heart trouble.

The objective manifestations revealed by examination of the patient on admission were as follows. The patient was a well developed and well nourished woman. She had congenital bilateral exophthalmos, an interpupillary distance of 83 mm and hyperplastic otitis media, bilaterally, with acoustic neuritis. The heart was of normal size, with an accessible left ventricle and an accentuated mitral second sound. The arterial pressures were variable, ranging from 146 to 280 systolic and from 88 to 130 diastolic.

Slight albuminuria was noted on several occasions. Chemical analysis of the blood revealed a hemoglobin content of 13 Gm per hundred cubic centimeters, an erythrocyte count of 4,370,000 and a leukocyte count of 5,300. The Wassermann reactions of the blood and the spinal fluid were negative. The basal oxygen consumption was 23 per cent above normal. Intrathecal pressures were normal, and tests of the cerebrospinal fluid gave normal readings.

Subsequent Course and Findings—The patient had repeated attacks of paroxysmal hypertension. The usual manifestations during an attack were aching of the feet, cold sweat appearing simultaneously over the entire body, generalized pallor, intense throbbing headache, precordial pain, shortness of breath, extreme fear of death, clonic contractions of the extremities, screaming, agitation, rapid pulse and elevation of arterial pressures. The paroxysms usually increased in intensity until they were terminated by the intravenous administration of sodium amytal (sodium isoamylethylbarbiturate). The electrocardiogram and blood sugar level were unaltered by paroxysms, and glycosuria and albuminuria did not occur. Intravenous pyelograms were normal. Roentgenographic studies of the chest, adrenal regions and gastroenteric tract revealed no abnormalities. The cold pressor test elicited a hyperreaction but did not produce an attack.

Perirenal insufflation of air was not attempted in this case, because it had been unsuccessful in the previous case and alarming symptoms had followed it.

The right adrenal region was explored through a posterior incision with the patient under anesthesia induced by means of avertin with amylene hydrate and cyclopropane. No abnormalities were found. The splanchnic nerve, however, was sectioned, and the first and second lumbar ganglions were removed. The patient's condition was not improved, and one month later the left adrenal region was explored. Although a tumor was not discovered, splanchnectomy and ganglionectomy were performed. The paroxysms of hypertension continued, and hysterical anesthesia of the entire left side of the body developed.

It appeared certain that the patient had a pheochromocytoma, but the two previous surgical procedures had failed to locate it, and two months later the hypertension became persistent. Section of the anterior and posterior roots of the thoracic nerves from the first through the fifth and destruction of the sympathetic tracts at the third thoracic level were decided on instead of an exploratory laparotomy. The arterial pressure declined to 138 systolic and 90 diastolic after the operation, and fluctuated between 110 systolic and 64 diastolic and 154 systolic and 100 diastolic. One paroxysmal attack occurred, two and a half months after the last operation, at which time the arterial pressures reached 195 systolic and 110 diastolic, but accompanying manifestations were mild. The subjective manifestations were almost entirely relieved. The headaches subsided and the vision improved, but a dull precordial distress continued. The patient stated that her health was better than it had been at any time during the past twenty years.

COMMENT

Paroxysmal hypertension is usually curable if it is diagnosed before irreparable vascular damage has occurred. Failure to comprehend the situation is, therefore, extremely unfortunate. The various manifestations described in the literature are listed in the accompanying table. The symptoms, however, are frequently similar to those accompanying functional anomalies. A history of paroxysmal attacks of peculiar sensations may be the only subjective manifestation. These peculiar sen-

*Manifestations of Paroxysmal Hypertension Which Have Been Described
in the Literature*

	Subjective	Objective
Neck	{ a Fulness b Choking c Swelling	Pallor followed by flushing of skin Cyanosis of nail beds
Substernal region	{ a Pressure b Pain c Peculiar feeling	Angiospasm of extremities and tip of nose Angiospasm of arterioles of ocular fundi
Epigastrium	{ a Fulness b Pain c Burning d Peculiar feeling	Hypertension Tachycardia or forceful cardiac impulse
Tingling of extremities		Epiphora
Blanching of extremities		Sialorrhea
Blanching of tip of nose		Glycosuria
Generalized sweating		Albuminuria
Pallor		Cylindruria
Nervousness		Hyperglycemia
Tremor		
Muscular weakness		
Palpitation		
Air hunger		
Headache		
Tinnitus		
Vertigo		
Epiphora		
Sialorrhea		
Nausea		
Vomiting		
Abdominal colic		
Diarrhea		
Constipation		
Polyuria		

sations may be located in the neck, the epigastrium or the substernal regions. When they occur in the neck, they are described as a sensation of fulness, choking or swelling, in the substernal region they may be identical with those accompanying angina pectoris, or may be only "peculiar sensations", in the epigastrium they may be described as actual pain or may suggest the possibility of a peptic ulcer. Angiospasm of the extremities and of the tip of the nose during an attack may well be confused with symptoms of Raynaud's disease. Other subjective manifestations which may be present during the paroxysms but are not likely to be elicited unless the possibility of paroxysmal hypertension is considered are sweating, pallor, nervousness, tremor,

muscular weakness, palpitation, headache, nausea, vomiting, vertigo, tinnitus, tingling of the extremities, air hunger, epiphora, abdominal colic and diarrhea. The duration of these paroxysms varies from only a few minutes to as long as twenty-four or forty-eight hours.

The physician is usually consulted between paroxysms at the time when objective manifestations are absent. If an attack should occur in his presence, the objective manifestations which may be observed are as follows: pallor followed by flushing of the skin, sweating, a reddish to a dusky blue discoloration of the finger nails, peripheral angiospasm of the extremities and nose, constriction of the arterioles of the ocular fundi, hypertension, either tachycardia or a slow forceful cardiac impulse, glycosuria, albuminuria, cylindruria and hyperglycemia. It is advantageous, therefore, to observe the patient during an attack. Patients occasionally observe conditions which will produce a paroxysm. Porter and Porter's¹⁷ patient could produce an attack by flexion of the body anteriorly and slightly to the left. Nuzum and Walton's³ patient noted that exercise before breakfast would initiate an attack, and MacKenzie and McEachern's¹⁴ stated that a blow on the abdomen would precipitate a paroxysm. Other patients know of no precipitating circumstances, therefore, methods for producing an attack are desirable. The injection of epinephrine used by Coller, Field, and Durant,⁶ and the cold pressor test used in our cases were both unsuccessful, whereas Nuzum and Walton's³ method of applying pressure over the carotid sinus was successful. These methods have been used in only a few cases, however, and further observations are indicated.

That paroxysmal hypertension may progress into the persistent variety has been suggested by Wells and Boman² and others, and a pheochromocytoma was discovered in a case of persistent hypertension described by Binger and Craig.¹⁰ The condition in our second case progressed into a persistent type, but the patient continued to have paroxysms during which the arterial pressures rose above the basal level. Although the presence of a pheochromocytoma in this patient is doubtful, there is sufficient evidence to indicate that certain patients with persistent hypertension may have had an initial paroxysmal variety, and therefore patients with persistent hypertension should be interrogated concerning previous paroxysmal manifestations.

The presence of a tumor in many of the reported cases has not been difficult to ascertain because of the presence of a palpable abdominal mass. In certain instances of smaller tumors deformities have been visible in the pyelograms. The tumor may be too small, however, to

17 Porter, M. R., and Porter, M. F., Jr. Report of a Case of Paroxysmal Hypertension Cured by Removal of an Adrenal Tumor, *Surg., Gynec. & Obst.* **50** 160-162 (Jan.) 1930.

after the pyelogram, or it may not be in close proximity to the kidney or even be in the adrenal region. If the pyelograms show no abnormalities, perirenal insufflation of air has been recommended by Mencher¹⁸ and Roome¹⁹. This procedure has not received general acceptance. Walters and Kepler²⁰ discontinued its use after three severe reactions had occurred. Fish²¹ abandoned the use of air after the occurrence of two fatalities from an embolism, but he stated that the procedure should not be condemned and that since the substitution of oxygen for air there have been no known fatalities. Mencher¹⁸ had no important reactions to it. Alarming reaction occurred in our patient after air insufflation by which the tumor was not visualized. This procedure has definite diagnostic possibilities, and its place as a diagnostic aid cannot be properly evaluated until there are further observations.

If the location of a tumor has not been ascertained by adequate urologic studies, by perirenal air or oxygen insufflation and by careful roentgenographic studies of the mediastinum, it is necessary to explore surgically the adrenal regions. It should be borne in mind, however, that the tumor may arise from aberrant glandular tissue and that therefore it may not be located in the adrenal region.

SUMMARY

The manifestations of paroxysmal hypertension have not been duly stressed. These manifestations and the diagnostic aids are therefore emphasized, and one case of proved and one of doubtful pheochromocytoma are reported.

18 Mencher, W. H. Perirenal Insufflation, *J. A. M. A.* **109** 1338-1341 (Oct 23) 1937.

19 Roome, N. W. Visualization of the Adrenal Glands by Air Injection, *J. A. M. A.* **111** 1061-1065 (Sept 17) 1938.

20 Walters, W., and Kepler, E. J. Surgical Lesions of Adrenal Glands, *J. A. M. A.* **111** 1061-1065 (Sept 17) 1938.

21 Fish, in discussion on Roome¹⁹.

CLINICAL VALUE OF DETERMINATION OF CHOLESTEROL ESTERS OF BLOOD IN HEPATIC DISEASE

CARL H GREENE, M D, P H D

RICHARD HOTZ, M D

AND

EVELYN LEAHY, A B

NEW YORK

The isolation of cholesterol from gallstones and its establishment as one of the characteristic components of the bile by Chevreul¹ focused attention on the changes in cholesterol metabolism in hepatic and biliary disease

The literature dealing with subsequent studies in cholesterol metabolism has been reviewed by McNee,² Campbell,³ Muller,⁴ Epstein,⁵ Klein⁶ and Hurxthal and Hunt⁷ There is a general agreement that the total cholesterol in the blood may be increased in disease of the biliary tract, especially in obstructive jaundice, whereas in parenchymatous hepatitis there is a fall to subnormal values

The interpretation of changes in the blood cholesterol in relation to hepatic disease and its use in the differential diagnosis of jaundice are rendered more difficult by the fact that many other disease processes, not necessarily involving the liver, influence the blood cholesterol Marked changes or variations from the normal are seen in such metabolic

From the Combined Medical and Surgical Clinic for the Study of Diseases of the Liver and Biliary Tract, New York Post-Graduate Medical School and Hospital

1 Chevreul, M Sur plusieurs corps gras V, Ann de chim (pt 5) **95** 40, 1815

2 McNee, J W Cholesterolin An Account of Its Relations to Pathology and Physiology, Quart J Med **7** 221, 1914

3 Campbell, J M H Cholesterol in Health and Disease, Quart J Med **18** 393, 1925

4 Muller, G L The Cholesterol Metabolism in Health and Anemia, Medicine **9** 119, 1930

5 Epstein, E Z Cholesterol Metabolism in Liver Disorders, Rev Gastroenterol **4** 12, 1937

6 Klein, W Ueber die enzymatische Hydrolyse der Cholesterinester des menschlichen Serums, Ztschr f physiol Chem **254** 1, 1938

7 Hurxthal, L M, and Hunt, H M Clinical Relationships of Blood Cholesterol with Summary of Our Present Knowledge of Cholesterol Metabolism, Ann Int Med **9** 717, 1935

diseases as diabetes mellitus and acute glomerulonephritis or nephrosis in endocrine disturbances such as hypothyroidism, hyperthyroidism and ovarian disturbances, in infection, regardless of the site, in anemia and in numerous other conditions

The cholesterol in the bile is present in the free state, while a considerable proportion of that in the blood is present in the esterified form Epstein,⁵ Klein,⁶ Hurxthal and Hunt,⁷ Thannhauser and Schaber,⁸ Sperry,⁹ LaRoche and Gigaut¹⁰ and others have advocated the determination of the ratio between the combined cholesterol (esters) and the total cholesterol as a test of hepatic function. They believe a decrease in the normal ratio, that is, a decrease in serum esters, is indicative of parenchymatous hepatic damage. Epstein,⁵ Sperry,⁹ and Paget and Pierrart¹¹ stated the belief that the ratio of the combined to the total cholesterol is a physiologic constant, which has been determined by these workers, as well as by Bloor¹² and Thannhauser,¹³ to be 65 to 75 per cent. A reduction in this proportion is evidence of hepatic damage. Further observations, both clinical and experimental, have shown that purely obstructive lesions of the extrahepatic bile ducts do not significantly change this ratio.

METHOD AND RESULTS OF CLINICAL STUDY

During the past four years we have intensively investigated the clinical value of the ratio of the combined to the total cholesterol. During this time 645 patients with possible disease of the liver or of the extrahepatic biliary tract have been investigated. It is our intention at this time to evaluate the results of this study in the light of the recent contributions by Epstein,⁵ Klein,⁶ Sperry,⁹ Nedswedski¹⁴ and others in an attempt to determine the clinical value of this ratio.

8 Thannhauser, S. J., and Schaber, H. M. Ueber die Beziehungen des gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion, *Klin Wchnschr* **5** 252, 1926.

9 Sperry, W. M. The Effect of Dextrose on the Cholesterol Functions of the Blood, *J Biol Chem* **116** 65, 1936, Concentration of Total Cholesterol in Serum, *ibid* **117** 391, 1937.

10 La Roche, G., and Gigaut, A. Nos connaissances actuelles sur la cholestérolémie et sa signification clinique, *Rev de méd, Paris* **54** 223, 1937.

11 Paget, M., and Pierrart, G. Nouvelle méthode de détermination du rapport esters du cholestérol/cholestérol total dans le sérum ou dans le plasma sanguin, *Compt rend Soc de biol* **126** 1206, 1937.

12 Bloor, W. R. Cholesterol in the Blood, *J Biol Chem* **24** 227, 1916, Diet and Blood Lipids, *ibid* **95** 633, 1932, The Lipoids of the Blood in Diabetes, *ibid* **26** 417, 1916.

13 Thannhauser, S. J. Die chemische Leistungen der normalen Leber für die Vorgänge des intermediären Stoffwechsels, *Klin Wchnschr* **12** 49, 1933.

14 Nedswedski, S. W. Ueber die Rolle der Gallensauren Salze bei der fermentativen Cholesterinestersynthese, *Ztschr f physiol Chem* **239** 165, 1936.

We must emphasize that our determinations have been on whole blood rather than on serum, which has been the accepted method in the literature. Therefore, our values will be found lower than the 65 to 75 per cent recorded as characteristic for normal serum. Whole blood was used to reduce the volume of blood required for making these chemical examinations and the numerous other ones required for a study of the blood. The method used was that of Bloor and Knudson¹⁵

During the period of study the routine chemical determinations on each patient were those for total and combined cholesterol, icteric index and van den Bergh reaction. After an intensive study and an adequate follow-up period 598 of 645 patients were found to have no apparent

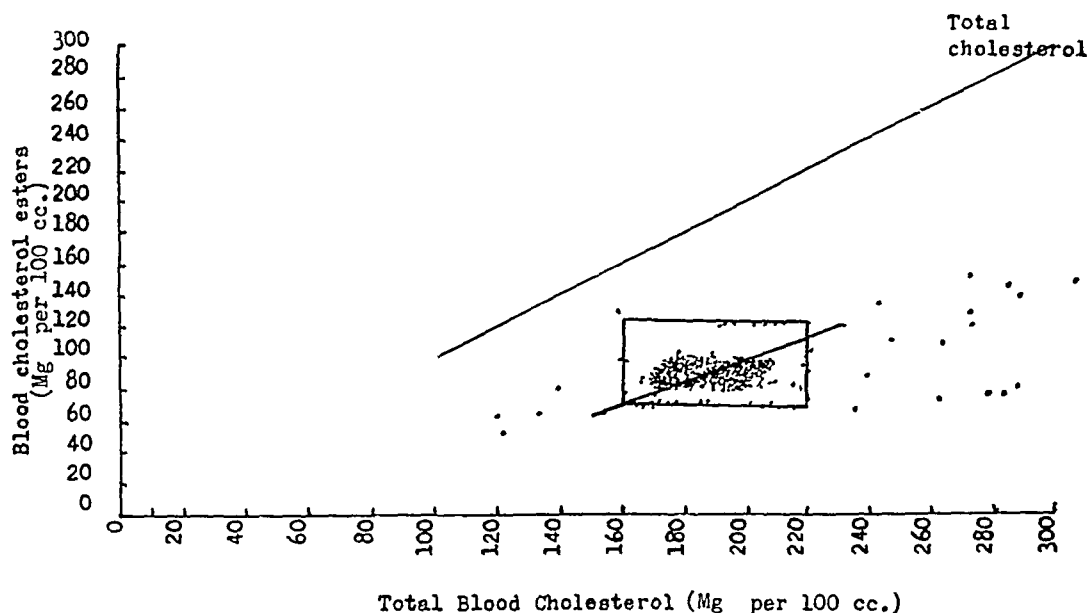


Chart 1—The range of cholesterol esters in the blood of patients without evidence of hepatic disease or jaundice

hepatic damage. This represented 92.7 per cent of all patients examined. In this group we found the normal range of total cholesterol to be 150 to 230 mg per hundred cubic centimeters and that of the esters to be 60 to 120 mg. The ratio of the combined to the total cholesterol was found to be 46 per cent plus or minus 6. This range, shown graphically in chart 1, clearly illustrates the constancy of our determinations. The upper oblique line represents the total cholesterol and the lower line is the median of the ester determinations. When the total cholesterol is much increased, the ratio no longer holds at 46 per cent, for the esters do not increase in proportion to the total cholesterol.

¹⁵ Bloor, W. R., and Knudson, A. The Separate Determinations of Cholesterol and Cholesterol Esters in a Small Amount of Blood, *J. Biol. Chem.* **27**: 107, 1916.

The frequency curves seen in chart 2 show the distribution of the total and combined cholesterol, respectively, in these normal patients. Of all the determinations on patients in this group, 88.2 per cent fell within this ratio. Only 4 per cent of all values for esters were lower than 60 mg per hundred cubic centimeters. On further analysis it appeared that in only 3 determinations out of 958 was the cholesterol ester total cholesterol ratio below 40 per cent when the esters were below the level of 60 mg per hundred cubic centimeters. We believe this to be a remarkable constancy for the ratio, especially in contrast to our results in patients with evident disease of the liver.

When compared with this uniformity in the values found for normal patients, the values for patients with hepatic damage and with clinical

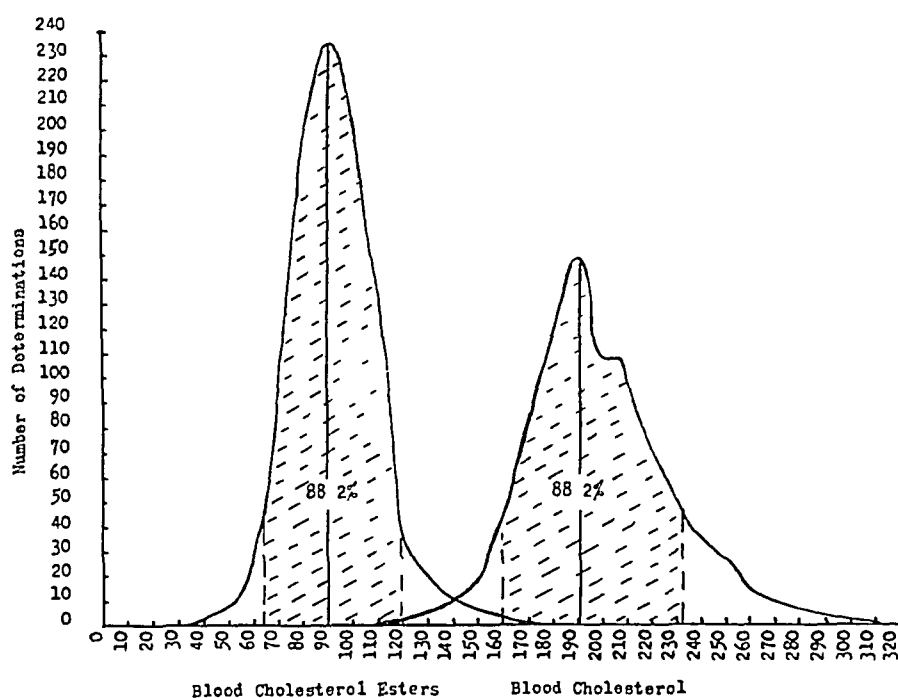


Chart 2—The frequency curves for cholesterol esters and total cholesterol determinations in the blood of patients without evident hepatic disease

jaundice showed marked abnormalities in the blood esters and in the ratio of the latter to the total cholesterol (chart 3). Forty-seven patients with proved disease of the liver or with biliary obstruction of extrahepatic origin were examined and studied. One hundred and fifty-four determinations of the total cholesterol and of the cholesterol esters in the blood were made on these patients to ascertain the diagnostic and prognostic value of the test.

Graphically, the results showed that there was a marked "shift to the left" of the values for patients with hepatic disease as compared with those for normal patients. The values for cholesterol esters in the blood of these patients were uniformly lower, and the ratio between the cholesterol esters and the total cholesterol was therefore decreased. In this

group there were 31 patients with hepatic disease. The latter showed the greatest decreases in esters. The esters were not definitely decreased in the 16 patients with obstructive jaundice, although the ratio had a tendency to be lower than the 40 per cent determined as the lower limit for our normal patients. An additional finding in this series was the

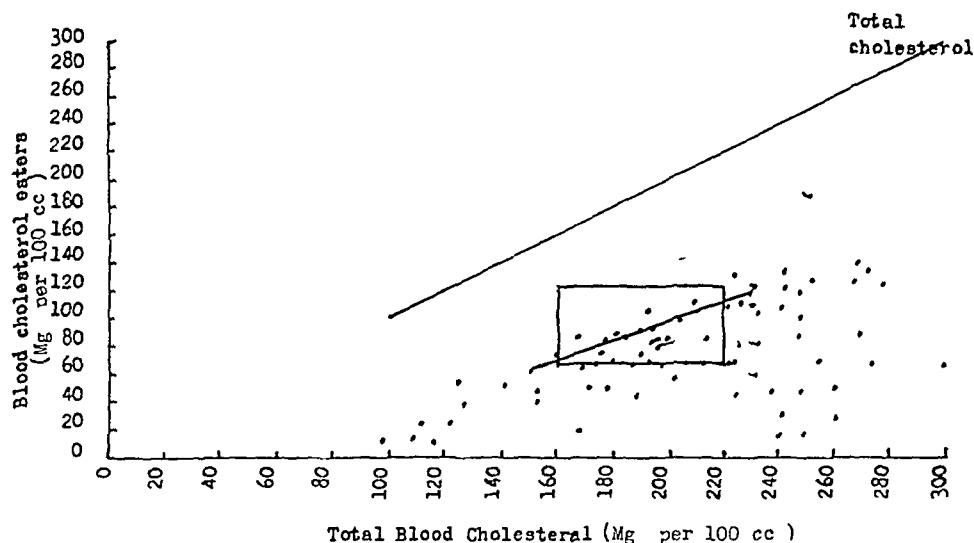


Chart 3—The range of cholesterol esters in the blood of patients with evident hepatic disease or clinical jaundice. The determinations to the left are predominantly those for patients with intrahepatic disease of the biliary tract, and those to the right, for patients with obstructive jaundice.

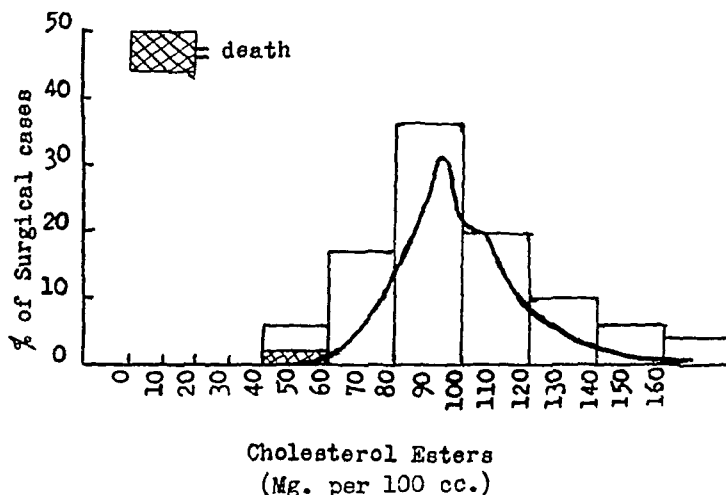


Chart 4—The cholesterol esters in the blood of surgical patients without evident hepatic disease as contrasted to the frequency curve of normal patients.

general increase of total cholesterol in the blood of patients with obstructive jaundice. No absolute differentiation was possible merely on the basis of this test, for mixed types of jaundice were frequently seen.

Values for Patients on Whom Operations Were Performed—Included in the general study reported were 92 patients on whom

operations were performed because of cholecystitis or cholelithiasis (chart 4). Seventy had normal physical, blood and operative findings in so far as the liver was concerned. In only 4 of these patients were the values of the cholesterol esters below 40 per cent of the total cholesterol. It is noteworthy that only one death occurred in this group of patients. The remaining 22 patients present an entirely different chemical picture so far as the blood cholesterol esters are concerned. When shown graphically (chart 5), there is a very definite "shift to the left" of the values for the cholesterol esters. All of these patients had jaundice due either to an incomplete extrahepatic obstruction or to definite hepatic injury. The general range for the total cholesterol corresponded to that found in normal patients, but the esters were reduced. Those patients with obstruction but without evident hepatic disease, 13 in number, had

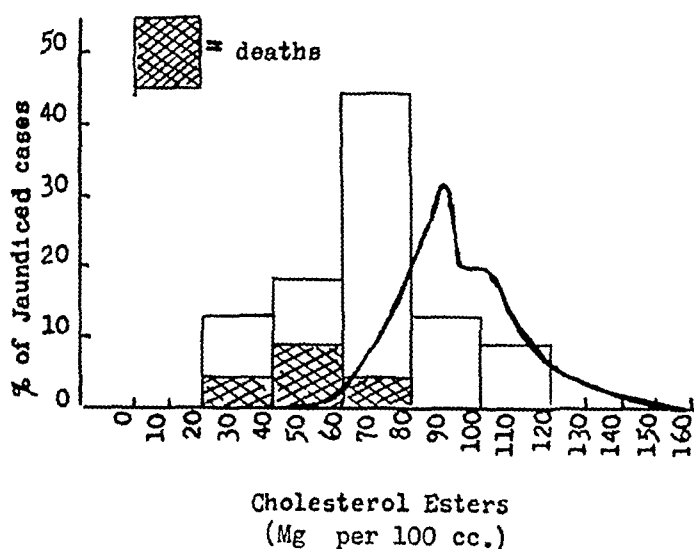


Chart 5—The cholesterol esters in the blood of patients with jaundice treated by surgical means and their mortality when contrasted with the frequency curve of the esters in normal patients

no remarkable change in the ester ratio. Those with hepatic damage as seen on biopsy and on operation, showed the greatest shift in this ratio. Four deaths occurred in this select group of patients that had low preoperative blood cholesterol esters.

In the accompanying table these patients are grouped according to the presence of jaundice and the ratio of the esters to the total cholesterol. It is apparent that patients with low cholesterol esters are poor operative risks.

Value of Determination of Cholesterol Esters in Prognosis—We have found a direct correlation between the values for the cholesterol esters and the prognosis and course of disease in the 47 patients with

evident hepatic damage. These patients fell roughly into two groups, that is, those in whom during the progress of their illness there was a steady increase in the cholesterol esters, and those in whom, in spite of treatment, the esters dropped until only a trace or none was found. In the former group recovery occurred in every instance, while in the latter a fatal termination was the rule. However, we have seen recoveries take place in 2 patients in whose blood only traces of esters were found for periods of ten and twelve days respectively.

Since such determinations do not lend themselves to a statistical study, we are presenting 6 representative case reports with graphs, showing the trend of the blood chemistry determinations. These case reports are representative of the results secured in this study.

CASE 1—When first seen in June 1932, M. M., a man, gave a history of pain in the upper part of the abdomen and moderate loss in weight. His liver was slightly enlarged, subclinical jaundice was present and his gallbladder was not

The Mortality After Surgical Operations on the Biliary Tract in Relation to the Combined Cholesterol Total Cholesterol Ratio

	No. Cases	Deaths
No evident hepatic disease or jaundice	70	1
Normal ratio	66	1
Low ratio	4	0
Clinical jaundice or evident disease of the liver	22	4
Normal ratio	13	0
Low ratio	9	4
Total in series	92	5

visualized on roentgen examination. The patient was kept under observation for twenty-one months, during that time ascites developed and his liver became palpable, but he showed no obvious jaundice. He died March 25, 1934, after an exploratory operation, at which time a Talma-Morison operation had been projected. Operation and autopsy revealed advanced hepatic cirrhosis.

Chart 6 shows the reduction in the cholesterol esters in the presence of hepatic damage, even though there was no jaundice or retention of bilirubin in the blood.

CASE 2—A. P., a white man aged 67, was admitted with a history of jaundice of five weeks' duration. He had fever, evidence of portal obstruction, ascites, a palpable liver and a deepening jaundice. He died three months after admission. Permission for autopsy was not obtained. All clinical evidence pointed to advanced hepatic cirrhosis, probably with an associated cholangitis.

Chart 7 shows the chemical determinations on the blood. It illustrates the prognostic importance of repeated ester determinations, and minimizes the importance of the total cholesterol values. The esters remained low in this patient in spite of a drop in the serum bilirubin and the icteric index.

CASE 3—S. B., a 26 year old white man, presented himself for hospitalization and gave a history of severe prostration, jaundice, nausea and vomiting of three days' duration after the intravenous injection of 0.6 Gm. of neoarsphenamine.

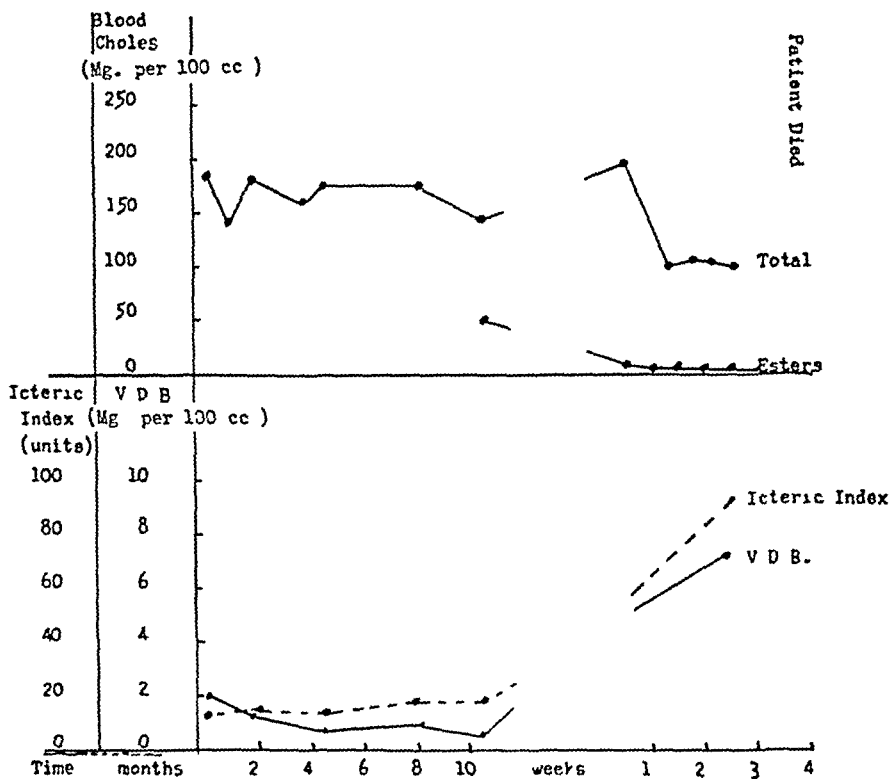


Chart 6—Chemical determinations on blood of a patient with biliary cirrhosis who died

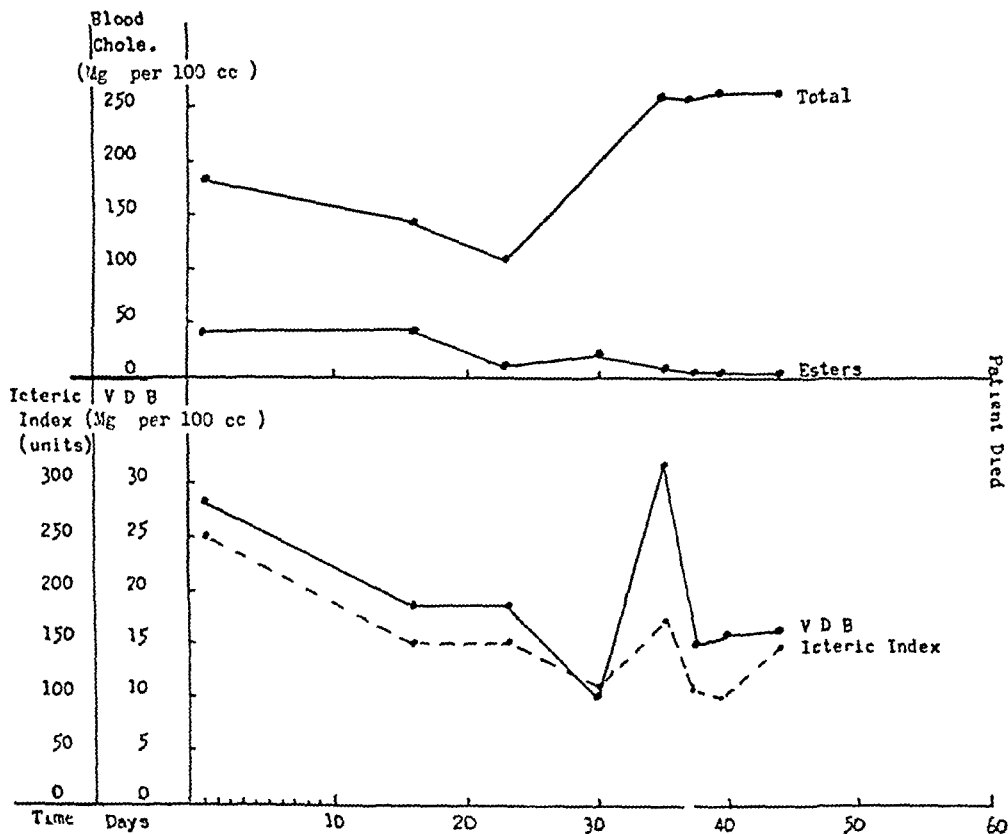


Chart 7—Chemical determinations on blood of a patient with biliary obstruction who died

He recovered with the administration of dextrose supplemented by repeated duodenal drainage. The course of the illness indicated that he had a severe toxic hepatitis.

Chart 8 shows the blood chemistry values, which initially presented the picture of a combined obstructive and parenchymatous jaundice. A favorable prognosis was indicated by the early rise in the esters.

CASE 4—S. H., a woman aged 40, was admitted to the hospital for cholecystectomy in July 1936 with a history of severe jaundice and colic. After operation her jaundice disappeared and the patient became symptom free for two

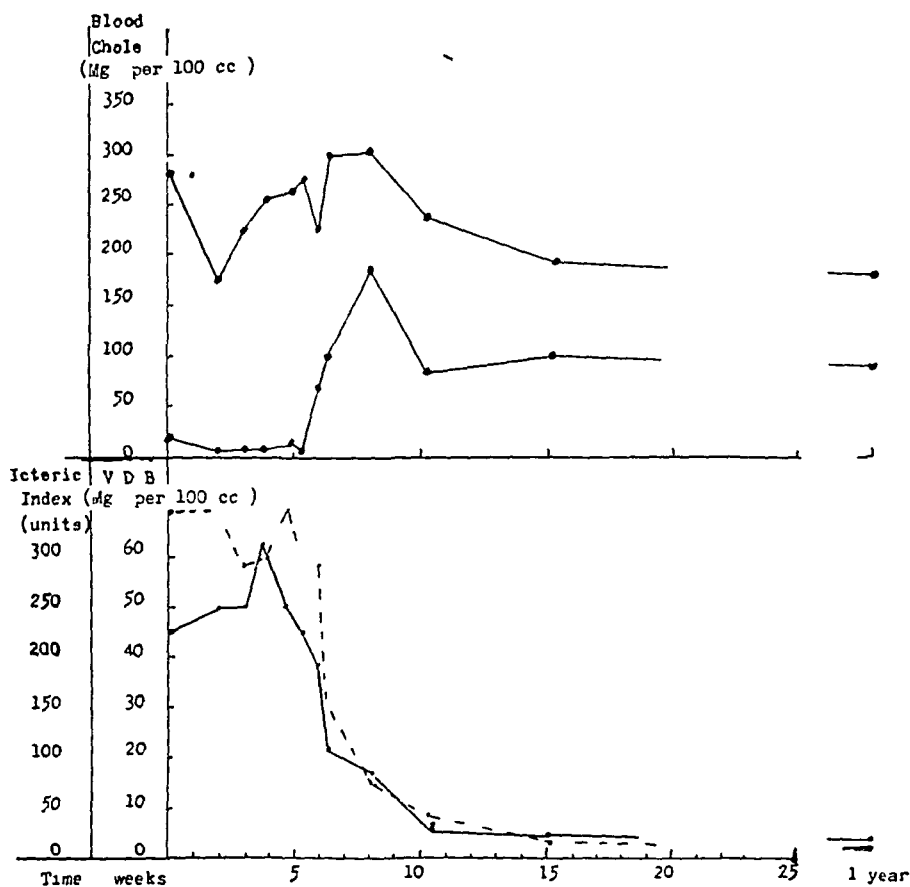


Chart 8—Chemical determinations on blood of a patient with severe toxic hepatitis who recovered

months, only to be readmitted for recurrent jaundice in December 1936. At operation stenosis of the common duct, with severe hepatitis, was noted. The patient died of shock (hepatic death?) twenty-four hours postoperatively.

Chart 9 shows how accurately the cholesterol ester values portrayed the true organic state of the liver. In this case, as in the preceding one, the high total cholesterol indicated an obstructive lesion rather than the mixed condition found at operation. The preoperative reduction in the intensity of the jaundice indicated by the icteric index gave a false security to the operative prognosis, which was not warranted by the steady drop in esters or by the pathologic condition found at operation.

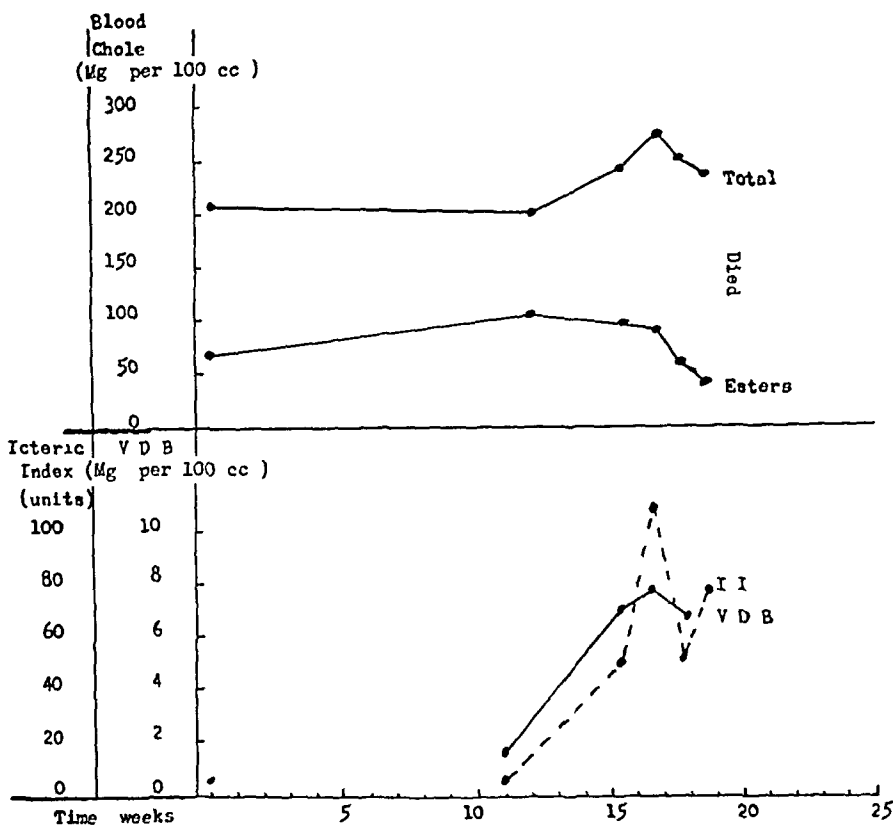


Chart 9—Chemical determinations on blood of a patient with obstructive jaundice complicated by severe hepatitis who died

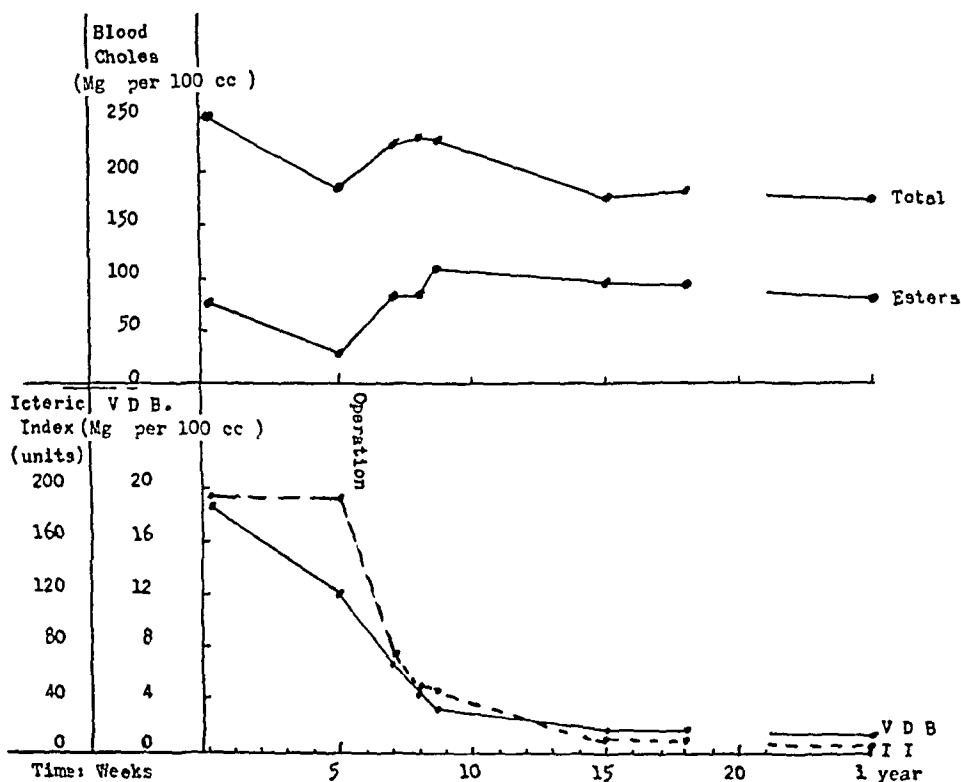


Chart 10—Chemical determinations on blood of a patient with biliary obstruction who recovered. Note the rise in cholesterol esters as the liver recovered its function

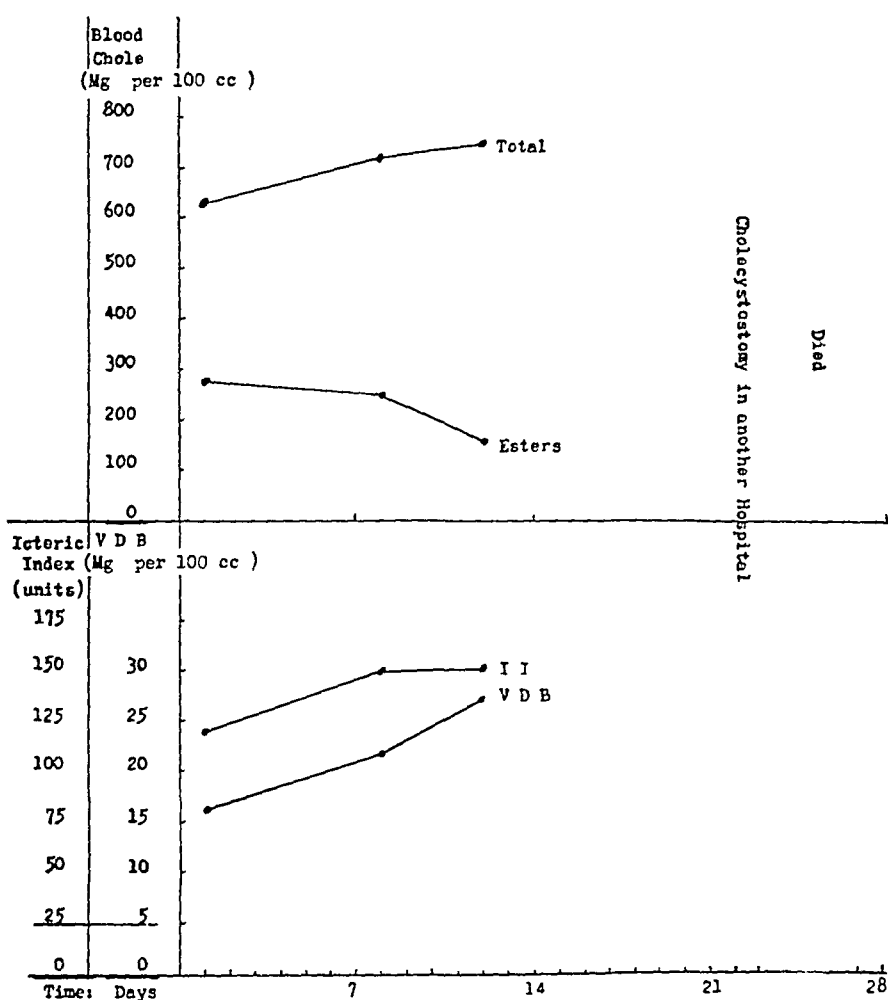


Chart 11—Chemical determinations on blood of a patient with obstructive jaundice due to carcinoma of the common duct who died

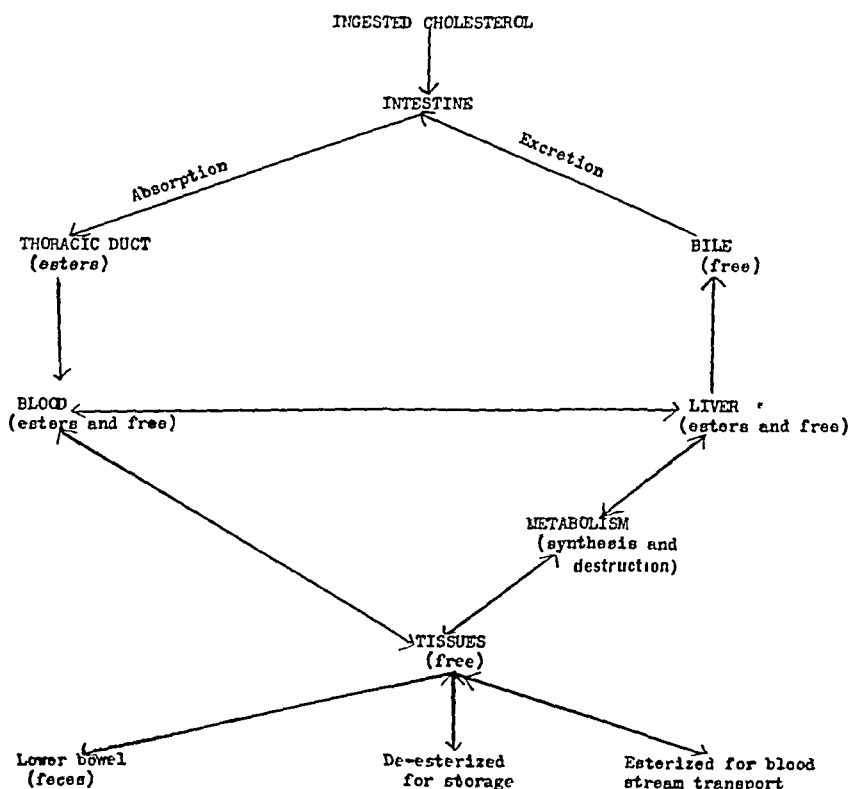


Chart 12—Present knowledge of cholesterol metabolism

CASE 5—A R, a white woman aged 41, presented herself in September 1937 with a history of jaundice of five weeks' duration, developing shortly after a cholecystectomy. She was dehydrated and had an enlarged liver and severe jaundice. Exploration revealed an enlarged, edematous, obstructed liver with complete atresia of the common duct just below the union of the hepatic ducts. A bilateral hepaticoduodenostomy was done and was followed by recovery.

Chart 10 shows the preoperative impairment of the hepatic function with return to normal on relief of the obstruction.

CASE 6—I A, a white man 65 years old, was admitted to the clinic in July 1937, with a history of increasing jaundice, pruritus, mild epigastric pain and loss of weight. He was markedly jaundiced and had a palpable liver, but there were no abdominal masses or tenderness. After study and observation, a diagnosis of carcinoma of the head of the pancreas was made and the patient was referred to his local hospital.

A cholecystectomy was performed Aug 7, 1937. The operative report read "The liver was intensely swollen and scarred. In the common duct, at the point of entrance of the ductus cysticus, there was a neoplasm which extended well up into the ductus hepaticus." The patient died immediately after operation, no autopsy was reported.

Chart 11 shows the chemical findings, which are characteristic for obstructive jaundice with superimposed hepatic damage. As the obstruction continued, the esters continued to drop. It is unfortunate that terminal studies could not be made on this patient.

DISCUSSION

The general course of cholesterol metabolism may be indicated schematically. The origin of the cholesterol esters in the blood and the regulation of the amount therein is still a source of controversy. That the blood contains an esterifying enzyme has been reported by Huber, Brown and Caset,¹⁶ Riegel, Ravdin and Rose,¹⁷ Vercellone¹⁸ and Klein,⁶ the latter also reported that esterification could be produced by extracts of the pancreas, liver, spleen and gastrointestinal tract.

Nedswedski¹⁴ further reported that bile salts were necessary for the esterification of cholesterol, and Chabrol and Sallet¹⁹ have reported parallel changes in the bile salts and cholesterol esters in the blood of

16 Huber, N J, Brown, G O, and Caset, A E. Prevention of Cholesterol Arteriosclerosis in the Rabbit by Use of Pancreatic Extract—Lipocatic, *Proc Soc Exper Biol & Med* **37** 441, 1937.

17 Riegel, C, Ravdin, I S, and Rose, H S. The Effect of Bile With and Without Cholesterol Esters in the Esterification of Cholesterol in Blood Plasma, *J Biol Chem* **120** 523, 1937.

18 Vercellone, A. Sulla esterificazione enzimatica delle sterine, *Biochim e terap sper* **25** 207, 1938.

19 Chabrol, E, and Sallet, J. L'hypercholesterolémie comme signe de gravité des cirrhoses, *J méd franç* **26** 280, 1937.

patients with hepatic disease Sperry⁹ and Klein,⁶ on the other hand, disagreed, they reported that bile salts inhibit cholesterol esterification

The importance of the liver in the regulation of cholesterol is disputed by Gardner and Gainsborough,²⁰ Burger and Habs²¹ and others on the ground that hepatectomized dogs do not lose the power of esterizing cholesterol but actually have an increased ester content in their blood Klein,⁶ however, described the synthesis of cholesterol esters by extracts of the liver Thannhauser and Schaber⁸ and Epstein⁵ in particular have insisted that the synthesis of cholesterol esters and the regulation of their level in the blood are a specific function of the liver

These views are so varied that without more definitive evidence one cannot describe the regulation of the cholesterol esters as a specific and exclusive function of the liver Our clinical experience is in accord with that previously reported by Thannhauser and Schaber,⁸ Epstein,⁵ Hurxthal and Hunt,⁷ Klein,⁶ and others, who indicated that in the presence of hepatic injury the cholesterol esters in the blood are reduced in amount or absent While a reduction of cholesterol esters is seen more frequently in parenchymatous than in obstructive jaundice, this reduction is of greater value as an indication of the severity of the hepatic damage than as an aid in differential diagnosis

The determination is of value in indicating an increase in the operative risk, and consequently a poor prognosis, in cases requiring surgical intervention While from a theoretic standpoint the determination may not be classified as a test of hepatic function, its value from a practical standpoint in the study of patients with hepatic disease has been established

SUMMARY AND CONCLUSIONS

The value for cholesterol in the blood of adults varies between 150 and 230 mg per hundred cubic centimeters whereas the combined cholesterol (esters) varies between 60 and 120 mg The ratio of the combined to the total blood cholesterol is quite constant—between 40 and 52 per cent

In this series, patients with evident hepatic damage had a decreased amount of combined cholesterol in the blood This decrease was sometimes but not always associated with a decrease in the total cholesterol The ratio, per se, was not of as great diagnostic usefulness as was the total amount of esters present in the blood

In uncomplicated obstructive jaundice the combined cholesterol tends to rise in proportion to the rise in total cholesterol, but in hepatic disease

20 Gardner, J H, and Gainsborough, H Blood Cholesterol Studies in Biliary and Hepatic Disease, *Quart J Med* **23** 465, 1930

21 Burger, M, and Habs, H Die alimentare Hypercholesterinämie beim stoffwechselgesunden Menschen, *Ztschr f d ges exper Med* **56** 640, 1927

the cholesterol esters tend to disappear from the blood regardless of the behavior of the total cholesterol

In a given case a progressive decrease in the values for the combined cholesterol of the blood signifies a poor prognosis, whereas a progressive increase signifies a good prognosis

The determination of the combined cholesterol of the blood is of great value in determining the prognosis of surgical treatment of patients with disease of the biliary tract

TREATMENT OF PNEUMONIA WITH SULFAPYRIDINE

OBSERVATIONS ON TOXIC REACTIONS

H K DETWEILER, M D

H I KINSEY, M B

W HURST BROWN, D M

AND

W R FEASBY, M D

TORONTO, CANADA

Since the appearance, in 1938 of favorable reports¹ on the use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) in the treatment of pneumococcic pneumonia, attention has been focused on this substance. Agreement on its usefulness has been general, but little mention has been made of the serious toxic manifestations which may attend its use. It is chiefly by reason of the latter fact that we are making a report on a small series of cases.

SELECTION OF CASES

Sulfapyridine became available in this hospital in October 1938,^{1a} at a time when we were still engaged in evaluating antipneumococcus rabbit serum in the therapy of pneumonia. This work was continued until mid-December. Until that time, therefore, patients with pneumonia were divided into three groups: those who were being treated with serum, those who were treated with sulfapyridine and controls. This accounts for the small number of patients treated with sulfapyridine up to that time. From mid-December 1938 until mid-February 1939 alternate patients with pneumococcic pneumonia received this drug. After February, in view of the encouraging results seen in our own clinic and those reported by others, it was decided to use sulfapyridine in the treatment of every patient with pneumonia, without reserving any as controls.

In the group of 18 patients with pneumococcic pneumonia treated during the period from October 1938 to February 1939 there was 1

From the Department of Medicine, University of Toronto, and the Medical Service, Toronto Western Hospital.

1 Evans, G M, and Gaisford, W F. Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine, *Lancet* **2** 14, 1938.

1a The sulfapyridine was provided by Messrs May and Baker, through Poulenc-Frères.

death The average total dose of the drug was 22 Gm , and it was found that the amount of drug free in the blood ranged from 2.5 to 11.8 mg per hundred cubic centimeters, the average amount being about 6 mg It was believed that these amounts were probably lower than the optimum, and therefore it was decided to increase the initial and the total dose so that each patient would receive an average of 35 Gm of sulfapyridine It was in the group of patients who received the latter amount that severe toxic manifestations were observed

In this analysis only those patients are included who were in the hospital over twenty-four hours, had pneumococci in the sputum and

TABLE 1—*Types of Pneumococci and other Bacteria in Sputum from Ninety Patients Treated with Sulfapyridine (Oct 1, 1938 to June 1, 1939)*

Organism	Patients	Deaths
Pneumococcus type I	11	1
II	10	0
III	4	0
V	2	0
VI	2	0
VII	3	0
VIII	3	0
XVI	2	1
XIX	1	1
XX	1	0
Undetermined	30	3
Mixed growths (<i>Bacillus influenzae</i> , <i>Friedlander's bacillus</i> and others)	8	1
<i>Staphylococcus aureus</i>	2	2
<i>Streptococcus haemolyticus</i> , beta type	9	2
Totals	88*	11

* In the other 2 cases in the group the specimens typed to group O and group D respectively, but the individual types could not be determined

In 2 cases *Str. haemolyticus* was found only by mouse inoculation, a pneumococcus, type not determined, having been present initially

In each of 2 cases pneumococci, type XXIII and type XXVI, respectively, were found coincidentally with hemolytic streptococci

received at least 10 Gm of the drug Patients with postoperative pneumonia are excluded

INVESTIGATION

On admission of a patient the history was taken, a physical examination, studies of the blood and a urinalysis were made, and any pneumococci present in the sputum were typed The diagnosis was confirmed serologically whenever necessary If the type of pneumonia was not revealed by the Neufeld method, mouse inoculation was done Bacteriostatic tests in sulfanilamide and sulfapyridine were carried out on organisms isolated from cultures of the sputum² Blood was taken from every patient on admission, and thereafter as indicated,

² This work was done by Mr D O Scott with the aid of a special grant from the Banting Research Foundation

for culture. During the administration of the drug daily white cell counts, hemoglobin estimations and urinalyses were made and careful records of the intake and output of fluids were kept. Chemical estimations of the total, free and combined sulfapyridine in blood and urine were made daily throughout this period. Patients whose sputum showed pneumococci of types I, II, III, IV, V, VII, VIII or XIV were given the Francis test with the type-specific polysaccharide (Lederle), until a positive result appeared.

Table 1, giving the types of pneumococci and other bacteria occurring in the sputum of these patients, is based on (a) Neufeld typings to pneumococcus type VIII from July to December 1938, (b) Neufeld typings to type XXXII from December 1938 on, and (c) mouse inoculations to bring out or confirm types, from February 1939.

THE BACTERIOSTATIC TEST

During the season 1938-1939, when sulfanilamide was tried on a controlled series of patients with type III pneumococcic pneumonia, a variation in the sensitivity of some strains of this pneumococcus to in vitro bacteriostatic tests was noted. It was therefore decided to carry out this investigation with sulfapyridine therapy, in order to discover whether there was any correlation between the clinical results of treatment and such tests.

In all cases in which the etiologic organism could be determined, the test was carried out as follows:

Wright's³ nutrient broth was used throughout except for the substitution recently, of some peptones, as suggested by White and Parker.⁴ Tubes were set up containing a solution of sulfanilamide or sulfapyridine in broth (from a stock solution containing 100 mg. per hundred cubic centimeters of broth) and sufficient broth added to give drug concentrations of 0.25, 1, 5 and 10 mg. per hundred cubic centimeters. Two drops of a 1:5,000 dilution of an eighteen to twenty-four hour broth culture was used in each tube. The bacteriostatic effect was estimated by the turbidity of the broth after twenty-four hours' incubation at 37.5 C.

Table 2 gives the results of bacteriostatic tests and shows how the minimal effective inhibition concentration varies with the two chemicals and with the various organisms. All the strains of pneumococci isolated were inhibited by both chemicals, but, as the table shows, there was great variation in the minimal concentration necessary to accomplish inhibition. We were unable to find any correlation between the bacteriostatic concentration in vitro and the effective concentration of the drug in the blood. In 1 instance *Staph. aureus*, and in 2

3 Wright, H. D. The Importance of Adequate Reduction of Peptone in the Preparation of Media for the Pneumococcus and Other Organisms, *J. Path. & Bact.* **37**: 257, 1933.

4 White, H. J., and Parker, J. M. The Bactericidal Effect of Sulphanilamide on Beta Haemolytic Streptococci in Vitro, *J. Bact.* **36**: 481, 1938.

instances the beta hemolytic streptococcus, was not inhibited by concentrations of either chemical up to 100 mg per hundred cubic centimeters

PLAN OF TREATMENT

Up to February 15, in addition to the routine treatment for pneumonia, each patient received sulfapyridine in approximately the dosage advocated by Evans and Gaisford¹. An initial dose of 2 Gm was followed in four hours by another 2 Gm, and then 1 Gm was given every four hours for six doses. On subsequent days this four-hourly dose was reduced 0.5 Gm per dose per day. From mid-February the

TABLE 2—*In Vitro* Bacteriostatic Effect of Sulfanilamide and Sulfapyridine on *Pneumococci* Isolated from Sputum

Pneumococcus Type	Frequency of Given Minimal Effective Bacteriostatic Concentration									
	Sulfanilamide					Sulfapyridine				
	Strains Tested	Concentration, Mg per 100 Cc				Strains Tested	Concentration, Mg per 100 Cc			
		0.25	1	5	10		0.25	1	5	10
I	20	6	3	9	2	21	3	3	11	4
II	9	2	3	4	0	9	2	0	6	1
III	14	9	1	3	1	13	6	2	2	3
IV	5	5	0	0	0	5	4	0	0	1
V	4	2	0	1	1	3	0	0	3	0
VI	4	2	0	1	1	4	1	0	2	1
VII	4	0	2	2	0	4	0	0	4	0
VIII	11	4	2	4	1	10	4	2	3	1
IX	2	1	0	1	0	2	1	0	0	1
XII	1	0	0	1	0	1	0	0	1	0
XIII	1	0	0	0	0	1	0	0	1	0
XVI	4	0	1	3	0	4	0	0	1	3
XVII	1	0	0	1	0	1	0	0	1	0
XVIII	2	1	1	0	0	2	1	0	1	0
XIX	1	1	0	0	0	1	0	1	0	0
XX	4	1	0	2	1	4	1	0	2	1
XXII	1	1	0	0	0	1	0	1	0	0
XXIII	2	1	0	0	1	2	1	0	0	1
XXVIII	1	0	0	1	0	1	0	0	1	0
XXIX	2	1	1	0	0	2	1	1	0	0
Not determined	10	7	1	2	0	10	3	5	2	0

doses were at four-hourly intervals but started with 2 Gm for six doses, then 1.5 Gm for six doses, then 1 Gm for six doses, and finally 0.5 Gm for six or more doses, to complete the course. This amount (at least 30 Gm) was given unless serious toxic manifestations occurred, in which case the drug was discontinued. Fluids were limited to 2,500 cc per twenty-four hours during the chemotherapy.

CLINICAL EFFECTS

After the ingestion of the first and second doses of sulfapyridine most patients began to feel more uncomfortable. The great majority experienced nausea and vomiting (see under "Toxic Manifestations"). If they persisted in taking the drug, there was usually a drop in temperature, pulse and respirations to normal within thirty-six hours.

This was maintained in 90 per cent of the patients, the remainder showing a rise in temperature and pulse after the course of treatment had been completed. This commonly indicated the onset of pleural effusion. During the afebrile period, while they were still receiving the drug, the patients suffered none of the distressing symptoms usually associated with pneumonia. They complained instead of the faintly bitter taste which the drug produces in the mouth, of the nausea and vomiting and, in a considerable number of cases, of profound exhaustion and weakness, which passed off when the treatment was completed.

COMPLICATIONS

Pneumococcic bacteremia was noted in 4 of the patients treated with sulfapyridine, all recovered.

Pleural effusion was noted in 8 patients with pneumococcic pneumonia, in 4 of whom it became purulent. Extension of the sulfapyridine therapy in the 4 remaining patients reduced the temperature once more, and the signs of effusion disappeared. A short summary of the 4 cases in which empyema developed follows.

CASE 1—Miss M. R., aged 17, was admitted to the hospital on Dec. 17, 1938. Pneumonia of the lower lobe of the right lung was well established. A serous pleural effusion was also present on the right side, and from it type I pneumococci were cultured. Repeated aspirations and sulfapyridine therapy failed to control the effusion, and the fluid gradually became purulent. On Jan. 5, 1939, closed drainage was initiated. This was later converted to open drainage. Several courses of sulfapyridine therapy were given and were poorly tolerated owing to the distressing nausea and prostration which were produced. In all, 63.5 Gm. was given. Several transfusions were necessary to offset the severe secondary anemia which gradually developed. The patient made a slow recovery.

CASE 2—Mr. R. B., aged 22, was admitted on March 3, 1939 and was discharged on May 3. On admission there was pneumonia of the lower lobe of the right lung, with type III pneumococci in the sputum. A right pleural effusion developed, which later became purulent in spite of repeated aspirations and the administration of 48 Gm. of sulfapyridine. Hemolytic streptococci alone grew from the purulent pleural effusion. Open drainage was performed on April 6, and a good recovery was made.

CASES 3 and 4—Both W. W. and W. S., aged 51 and 21, had type III pneumococci in the sputum, and pleural effusion developed in both. *Staph. aureus* of the hemolytic type and pneumococcus type III were cultured from the effusion. These organisms were inhibited in vitro only by concentrations as great as 100 mg. of sulfanilamide or sulfapyridine per hundred cubic centimeters. These patients received 45 and 50 Gm. of the drug, respectively, and the pleural effusions were repeatedly aspirated but finally required open drainage. Both patients made good recoveries.

TOXIC MANIFESTATIONS

This is primarily a report on 70 patients who were treated for pneumococcic pneumonia with sulfapyridine, but conclusions as to the

toxicity of this drug may be properly drawn from a consideration of all the patients so treated. The following remarks are therefore based on the results in the 90 patients who received the drug. Eighty-five per cent of these patients suffered some toxic manifestations.

Mild Toxic Manifestations—1 Nausea and Vomiting. Nausea occurred in 80 per cent and vomiting in 78 per cent of the 90 patients. In about 10 per cent the vomiting became a serious obstacle to adequate treatment. Among the many unsuccessful means used in the attempt to overcome this troublesome symptom were a powdered form of the drug, given in fruit juice or milk, antacids, a duodenal tube for administering the drug and food.

There are grounds for believing that the nausea and vomiting may be due in part to the local irritation set up by the drug in the stomach. Some patients vomit the tablets a few minutes after swallowing them. On the other hand, patients treated by intravenous injection of the sodium salt of sulfapyridine not infrequently experience nausea and vomiting. This suggests that at least part of this toxic manifestation originates from the central nervous system. Trial of ascorbic acid to control this symptom was unsuccessful. Nicotinic acid has been shown⁵ to be effective in controlling the sickness following high voltage roentgen therapy. One of us (W. H. B.) found that the anorexia, nausea, vomiting and depression and to some extent the cyanosis were often remarkably diminished by oral administration of 100 to 300 mg. of nicotinic acid in each twenty-four hours. (This was an independent observation. Priority, however, belongs to Dr. A. P. McGinty, whose work has since come to our notice⁶.) Since March 1939 nicotinic acid has been given in divided doses (50 mg. every four hours) to alternate patients receiving sulfapyridine. Twenty patients have been treated in this way, of these, 12 were nauseated and 8 vomited, but the severity of each symptom has been much less than in the controls of this group or in the series as a whole. Anorexia, in particular, seems to be much less severe in the patients receiving nicotinic acid. The results are sufficiently encouraging to warrant further trial.

Just how nicotinic acid acts in this connection is not yet fully understood. It has been found⁷ that pellagrins have an excess of porphyrin in the urine, which has been reduced to normal by the administration of nicotinic acid. However, it would seem from recent work by Graham⁵ that the degree of radiation sickness and of the response to nicotinic acid

⁵ Graham, J. W. Radiation Sickness. Treatment with Nicotinic Acid, *J. A. M. A.* **113** 664 (Aug. 19) 1939.

⁶ McGinty, A. P., Lewis, G. T., and Holtzclaw, M. R. Symptoms Occurring with Sulfanilamide Relieved by Nicotinic Acid, *J. M. A. Georgia* **28** 54, 1939.

⁷ Spies, T. D., Cooper, C., and Blankenhorn, M. A. The Use of Nicotinic Acid in the Treatment of Pellagra, *J. A. M. A.* **110** 622 (Feb. 26) 1938.

are not related to porphyrin excretion. After the work of Rimington⁸ on the pigment metabolism after administration of sulfanilamide and related compounds, Graham suggested that in radiation sickness the abnormal porphyrin excretion is due to disturbance of hemopoietic or of hepatic function. This may be the case also with sulfapyridine, and further studies on this problem are necessary.

At the suggestion of Dr. Alexander Fleming and his associates at St. Mary's Hospital, London, we have since tried giving sulfapyridine as an emulsion (1 Gm. of the powdered drug suspended in 1 drachm [3.88 Gm.] of half strength mucilage of tragacanth B. P.) and have obtained better results than any obtained hitherto. Since we believe that the nausea and vomiting are of both central and local origin, we advise combining the administration of the drug in the form of an emulsion in mucilage of tragacanth with the administration of 30 to 50 mg. of nicotinic acid for each dose of emulsion.

2 **Anorexia** This symptom without nausea and vomiting was observed in 4 patients but seemed of no consequence except that it made the patients loath to take the drug. It was alleviated by the use of nicotinic acid.

3 **Headache** This is an uncommon symptom. It does not seem to occur with much greater frequency than in patients whose pneumonia is treated symptomatically.

4 **Dizziness** This occurred in 6 patients but was not serious.

5 **Cyanosis** This symptom was present in 8 patients. In 1 instance, sulfhemoglobinemia was detected spectioscopically. This condition occurred when the level of the free drug in the blood was 14.9 mg. per hundred cubic centimeters.

6 **Facial twitching** This symptom was noted in 3 patients. It occurred when the level of the free drug in the blood was high, about 15 mg. per hundred cubic centimeters, and was not of any special significance.

Serious Toxic Manifestations—The following symptoms were considered indications for either partial or complete withdrawal of the chemotherapy.

1 **Oliguria** Oliguria was considered to be present when less than 300 cc. of urine was excreted in twenty-four hours. This complication developed in 9 cases. In these the administration of the drug was

⁸ Rimington, C., and Hemming, A. W. Porphyrinuria Following Sulphanilamide. Sulphanilamide Dermatitis, *Lancet* **1** 770, 1938. Rimington, C. Disturbance of Pigment Metabolism Following Administration of Drugs of the Sulphanilamide Series and Simpler Related Substances, *Proc. Roy. Soc. Med.* **32** 351, 1939.

discontinued, and fluids were given in large amounts by mouth and intravenously

2 Anuria This symptom occurred in 3 patients

Mr H F, aged 77, had bronchopneumonia at the base of the left lung with pneumococci (the type of which could not be determined) in the sputum. During the course of treatment and in spite of efforts to combat developing oliguria by forcing fluids, he suffered a sharp drop in the white cell count and in hemoglobin, gross hematuria and, later complete anuria. The level of the free drug in the blood was 16 mg per hundred cubic centimeters. As a result of intravenous administration of fluids and complete withdrawal of the drug, this man made a gradual recovery, no renal impairment being demonstrable.

Mr J R, aged 58, was admitted March 9, 1939 and died April 1, 1939. On admission he had bronchopneumonia of the right lung with pneumococci (type not determinable) in the sputum. (Cultures from the lung at autopsy showed hemolytic *Staph aureus*.) He was given 23 Gm of sulfapyridine and he became afebrile in four days. The temperature rose again and a second course of the drug was given (48 Gm in fourteen days). On the fourth day of this course a macular rash developed, which disappeared without special measures except the interruption of chemotherapy for one day. While he was still receiving the drug (6 Gm daily) oliguria developed (210 cc of urine in twenty-four hours), then, for a short time, he was anuric. Fluids relieved the condition, and the administration of the drug was continued (3 Gm daily). Several days later the white cell count was 2,000, and the administration of sulfapyridine was discontinued. In spite of intravenous administration of fluids, blood transfusions and intramuscular injections of liver extract, the white cell count fell to 700, and agranulocytosis was present. Autopsy showed lobar pneumonia, coronary sclerosis, arteriosclerotic kidneys, slight atrophy of the pancreas and a fatty liver.

Mr W P, aged 19, was admitted April 16, 1939 and died April 19, 1939. Pneumococci (type XXIII) were found in the sputum, and later, after mouse inoculation, hemolytic *Staph aureus* was identified. Sodium sulfapyridine was administered intravenously to a total of 152 Gm, and complete anuria developed during the last ten hours of life.

The significance of the oliguria is discussed, and the details of the case of W P are reported, elsewhere⁹. Briefly our experience led us to the conclusion that the use of heavy doses with restriction of the fluid intake is a procedure seldom justified, and one attended by serious risks.

3 Gross hematuria

In 6 patients gross hematuria occurred, associated in 4 with pain in the costovertebral angle. The concentration of the free drug in the blood of these 6 patients varied from 10 to 27 mg. It may be that the hematuria is due to precipitation of crystalline sulfapyridine in the renal tissue, as these crystals are not infrequently seen in the urine when concentrations of the free drug are high. In none of these patients was impairment of renal function detected subsequently.

4 Leukopenia

A white cell count of less than 4,500 was recorded for 8 patients. Of these, J R, already referred to, was the only one in

⁹ Brown, W H, Thornton, W B, and Wilson, J S. Observation on the Absorption, Distribution and Excretion of Sulphapyridine, Dagenan or M & B 693, *J Clin Investigation* 18 803, 1939.

whom the condition resulted in a fatality. Leukopenia was found in patients showing 3 to 11 mg of the free drug per hundred cubic centimeters of blood. In all these patients there was relative granulopenia, and in the patient whose condition ended fatally agranulocytosis developed.

5 Anemia. Six patients had a sharp drop in hemoglobin and in red cells during the five days of treatment. The average drop in hemoglobin was 14 per cent, and the average decrease in red cells was 700,000. No special measures were adopted to remedy this condition, and recovery was spontaneous. (Details of the blood dyscrasias are given elsewhere¹⁰.)

6 Cutaneous rashes. A fine macular to morbilliform rash developed in 6 patients. One of these was J. R., already referred to, who had a rash two weeks before death. Another, W. L., aged 31, was admitted on Feb. 9, 1939, with pneumonia of the lower lobe of the right lung and type III pneumococci in the sputum. He was much nauseated by the sulfapyridine, and on the fourth day of therapy a maculopapular rash and cyanosis developed. He made a good recovery and returned to work, but he was readmitted on March 3, 1939, again with pneumonia of the lower lobe of the right lung. The sputum contained type V pneumococci on this occasion. A scarlatiniform rash developed on the third day of chemotherapy, and there was a sharp drop in hemoglobin and red cells. Cessation of the therapy and forcing of fluids brought about a disappearance of the toxic manifestations, and the patient made a satisfactory recovery.

7 Thermal reactions. In a few instances withdrawal of the drug apparently resulted in a reduction of the temperature a point or two, to normal. It was difficult to ascertain whether the fever had been due to the drug because the drop in temperature usually occurred about the eighth day of the pneumonia and may have been due to the fact that the febrile phase of the illness happened to cease on that day. There were, however, 5 instances in which a fever frankly due to the effect of the drug was encountered.

8 Mental changes. Some patients seemed to become more restless and confused during treatment with sulfapyridine. It was difficult to determine the cause of extreme drowsiness or of delirium, as such manifestations are common in severe pneumonic conditions, but in 4 fatal cases there was a question of whether these states had been accentuated by treatment, especially since the levels of the drug in the blood were high.

10 Morgan, J. R. E., and Detweiler, H. K. Hematologic Study of Seventy-Six Pneumonia Cases Treated with Sulfapyridine Including a Fatal Case of Agranulocytosis, *J. Lab. & Clin. Med.* 25: 275, 1939.

Table 3 is designed to show the relation of toxic manifestations to the total dose of sulfapyridine. Nausea and vomiting are omitted from the list of symptoms because the incidence of these symptoms was reduced by the use of nicotinic acid.

Concentrations in the Blood—The average maximum blood level of the free drug was about 9 mg per hundred cubic centimeters. In patients recovering the levels ranged from 3 to 25 mg. In those who died the levels ranged from 5.8 to 28.3 mg. A detailed study of the absorption and distribution of the drug in the tissues has been published elsewhere.⁹

Intravenous and Intramuscular Sulfapyridine Therapy—In February 1939 supplies of sodium sulfapyridine (Calco) were obtained through Dr. Perrin Long, of the Johns Hopkins Hospital. Later,

TABLE 3—Relative Frequency of Serious Toxic Manifestations with Two Schemes of Dosage of Sulfapyridine

	Lower Doses (Average Total 22 Gm.)	Higher Doses (Average Total 35 Gm.)
Average free drug in blood, mg. per 100 cc.	7	10
Patients	21	69
Number with given toxic manifestations		
Oliguria	0	9
Anuria	0	3
Gross hematuria	1	5
Leukopenia	2	6
Agranulocytosis	0	1
Anemia	0	6
Rash	1	5
Fever	1	4
Deaths	2	9

sodium sulfapyridine was supplied by Poulenc-Frères for intravenous use. Patients treated by the intravenous method are reported on in detail elsewhere.⁹ Our experience has as yet been limited, but it would seem that this method of administration should be used only when patients cannot be treated by mouth. When patients were very ill, treatment was begun with an intravenous injection of 70 cc. of a 5 per cent solution (3.5 Gm.). This was later supplemented by further intravenous medication at eight hour intervals or by oral therapy every four hours. The dosage was carefully controlled by clinical and laboratory observations, including chemical estimations of levels of the free drug in the blood. For intravenous use a 5 per cent solution of the drug supplied by Poulenc-Frères was made up with distilled water from the ampules, which contained a 33 per cent solution. For intramuscular use we injected initially 6 cc. of the 33 per cent solution (2 Gm.), directly into the gluteal muscles. This was followed in eight hours by an injection of 1 Gm. into the opposite hip, and a similar dose was given at eight hour intervals until the level of the free drug in the blood was 8 mg.

or until the patient could take sulfapyridine by mouth. The 33 per cent solution had a p_H of approximately 11.3, and it was remarkable that no great discomfort was occasioned by the injection into the gluteal muscles. An explanation for this may be the small size of the molecule of sodium sulfapyridine.

MORTALITY

Five of the 70 patients who were treated with sulfapyridine died, giving a mortality rate of 7.1 per cent. The following brief summaries will serve to show the type of case in which this chemotherapy was unsuccessful.

1 Mrs. G. T., aged 60, was admitted on Dec. 30, 1938 and died on Jan. 20, 1939. This woman had bilateral bronchopneumonia, with type XVI pneumococci in the sputum, associated with diabetes mellitus and hypertensive cardiovascular disease. Despite the administration of 24 Gm. of sulfapyridine, with the blood levels reaching 11 mg. per hundred cubic centimeters, she never became afebrile. In vitro, the type XVI pneumococcus isolated from the sputum showed bacteriostasis in the presence of 5 mg. of drug per hundred cubic centimeters. At autopsy marked congestion of the lower lobes was noted, but the pneumonia had resolved. There were areas of infarction in the liver and spleen, and a uterine abscess was found.

2 Mrs. H. V., aged 75, was admitted on March 13, 1939 and died on March 29, 1939. The diagnosis on admission was bronchopneumonia of the lower lobe of the right lung, for which she was given sulfapyridine in the routine doses described, so that a blood level of 14 mg. per hundred cubic centimeters was reached. She did not become afebrile. There were pneumococci (type not determinable) in the sputum. Despite continued chemotherapy this pneumonia did not resolve, and the patient died without extension of the disease or development of any complication. At autopsy diffuse bronchopneumonia of the lower lobe of the right lung was noted, together with fibrosis of the heart, acute ulcers of the stomach and moderate fatty degeneration of the liver.

3 Mr. G. B., aged 63, was admitted on March 14, 1939 and died on March 23, 1939. This man had parkinsonism and bilateral bronchopneumonia. The blood levels of free sulfapyridine reached 14 mg. per hundred cubic centimeters with the regular dosage described, but the patient's course was steadily downward. Autopsy revealed marked engorgement of the lower lobes of both lungs and moderate fatty change within the liver. There was marked sclerosis of many blood vessels, especially of the aorta.

4 Mr. H. W., aged 70, was admitted on March 17, 1939 and died on March 23, 1939. This man was admitted to the hospital with a fractured pelvis, and three days later bronchopneumonia developed. This did not respond to 33 Gm. of sulfapyridine, although the blood levels of the drug reached 10.4 mg. per hundred cubic centimeters. Supportive therapy and oxygen were of no avail. Permission for autopsy was refused.

5 Mr. C., aged 70, was admitted on April 21, 1939 and died on April 30, 1939. Bronchopneumonia of the lower lobe of the right lung was present on admission, and pneumococci (type XXVI) were found in the sputum. In spite of the administration of 17 Gm. of sulfapyridine, his condition grew steadily worse, the pneumonic signs persisted and the patient died. Permission for autopsy was refused.

Attention is called to the fact that the average age of those who died was 68 years, none were under 60 years of age

NONPNEUMOCOCCIC PNEUMONIAS TREATED WITH SULFAPYRIDINE

There were 15 patients in this group, of these, 6 died. The organisms found were distributed as follows

	Patients	Number Who Died
Mixed Friedlander's bacillus, etc	6	1
Hemolytic streptococci of the beta type	6	2
Hemolytic Staph aureus	3	3

One of the patients who died from pneumonia caused by the beta hemolytic streptococcus deserves special mention

Mr R Y, aged 19, was admitted on March 13, 1939 and died on March 23, 1939. He had a well developed pleural effusion on the right side, beta hemolytic streptococci were cultured. Repeated aspirations and the administration of 33 Gm of sulfapyridine (level of free drug in the blood, 189 mg per hundred cubic centimeters), failed to control the process. The pulse became very rapid, and the blood pressure fell in spite of stimulants. The patient died two days after an open drainage of the pleural cavity. Permission for autopsy was refused.

COMMENT

Our experience with the use of rabbit serum had previously led us to the conclusion that it has a definite place in the treatment of pneumonia.¹¹ The death rate among patients treated with serum up to the time of writing has been 10 per cent, as compared with a rate of 25 per cent in the control group over a period of five years. This rate is not significantly different from that among patients treated with sulfapyridine, as here reported. It must, however, be remembered that in our hands the use of serum has been applicable to only about 50 per cent of all patients with pneumonia, whereas sulfapyridine, by virtue of its polyvalency, was used in a much wider field. There can be no question of its value in the treatment of all types of pneumococcic pneumonia. Of outstanding importance is the time saved, because this form of specific treatment can be begun while one is waiting for bacteriologic identification of the causal organism. This is especially apparent in those cases in which sputum is not immediately available.

A definite statement as to the optimum concentration of sulfapyridine in the blood cannot as yet be made, but in general an initial level of 6 mg per hundred cubic centimeters and a maintenance level of 3 to 4 mg should be the goal. Patients were encountered whose treatment

11 Kinsey, H I, Brown, W H, and Feasby, W R. Antipneumococcus Serum Treatment of Pneumonia, *Canad Pub Health J* **31** 56, 1940

had to be discontinued after the first day because of the toxicity of the drug. Some of these made an uneventful recovery without further treatment. In others (particularly those with pneumonia caused by pneumococcus type III) the disease could not be controlled unless high concentrations were established. Resistant conditions could not be determined by reference to bacteriostatic tests as stated in an earlier section of this paper. From October to February, a period during which the modified Evans and Gaisford dosage was used, 2 deaths resulted in 21 patients. In 18 of these the pneumonia was pneumococcic, and 1 of these patients died. After this time larger doses were used, without any improvement in the mortality rate. Among the 21 routinely treated patients in the control series there were 4 deaths.

Undoubtedly the biologic factor (the state of the immunity mechanism) has a very important role in determining how much chemotherapy should be employed and for how long. It was hoped that the Francis test would throw some light on this problem. In a few cases it was of definite aid in demonstrating that an excess of circulating antibodies was present, and in these cases discontinuance of the drug was not followed by exacerbations. The usefulness of this test was unfortunately obscured by the high percentage of positive results obtained on patients at the time of admission to the hospital. Agglutination tests were not used in this investigation, but it seems reasonable to anticipate that a test indicating the time at which the biologic immunity has become fully mobilized would prove to be of very considerable aid in chemotherapy. In any event, the importance of active immunity should not be lost sight of in the treatment of pneumonia. It is our belief that sulfapyridine is of extraordinary value in that it permits treatment to be instituted at once, when the pneumococcus is identified, serum may be used as an adjuvant. Such a method, in which the total dose of sulfapyridine is reduced, may well prove to be the one of choice.

During the period of moderate dosage (October to February) few serious effects were observed, despite the fact that in 2 cases chemotherapy was prolonged. After this period, and coincidental with the institution of more intensive dosage, higher levels of the free drug in the blood were attained, and the occurrence of serious toxic effects became frequent. Hematuria, oliguria, anuria, leukopenia, rashes and fever, which were previously infrequent or not observed, now appeared. This series stands in contrast to almost all those already published in the large number of toxic manifestations observed. On the other hand, the mortality rate noted here is slightly higher than many of those reported elsewhere. The conclusion is inescapable that the high blood levels reached in the latter part of the season did not offer a better protection against death from pneumonia and that the occurrence of serious and

frequent toxic manifestations was directly due to the adoption of heavier doses. The average total and daily doses in the earlier period were, respectively, 22 and 5.5 Gm, those in the later period were 35 and 7.5 Gm. These small differences emphasize the narrowness of the range between doses which are effective and those which are attended by risk of serious toxicity.

SUMMARY

1 The treatment of pneumococcic pneumonia with sulfapyridine resulted in this series in 5 deaths in 70 patients. The average age of those who died was 68 years.

2 Sulfapyridine therapy did not reduce the incidence of complications of pneumonia in this small series.

3 In this series 85 per cent of 90 patients who received the drug had toxic manifestations. The earlier dosage (average total dose, 22 Gm) was relatively innocuous, but the later dosage (average total dose, 35 Gm) was attended by many serious toxic manifestations, without lowering of the death rate. Until more is known of the concentration of sulfapyridine in the blood which is effective in combating pneumococcic pneumonia, heavy doses should be employed with great caution.

4 Nicotinic acid was found to be effective, to some extent, in controlling the nausea and vomiting which occurred in 85 per cent of the patients receiving sulfapyridine. Vomiting was also reduced when the drug was given as an emulsion, the powder suspended in mucilage of tragacanth.

5 The reduction of the fluid intake to less than 2,500 cc when heavy doses were employed was observed to cause acute renal insufficiency, resulting in oliguria and anuria.

6 No correlation between *in vitro* bacteriostatic tests and clinical results with sulfapyridine could be shown.

7 Sulfapyridine was unsuccessful in the treatment of streptococcic and staphylococcic pneumonia.

PURPURA HAEMORRHAGICA FOLLOWING NEOARSPHENAMINE AND BIS- MARSEN THERAPY

FURTHER STUDIES ON SENSITIVITY TO ARSPHENAMINE
AND TOLERANCE TO MAPHARSEN

ERNEST H FALCONER, M D

AND

NORMAN N EPSTEIN, M D

SAN FRANCISCO

In 1936 studies on 3 patients with purpura haemorrhagica following neoarsphenamine therapy were reported ¹ We ascertained by experiments that 2 of these patients were very sensitive to neoarsphenamine but apparently not sensitive to mapharsen, as the intravenous injection of this arsphenamine derivative failed to produce any significant effects on the platelets and capillaries or any untoward constitutional reaction The third patient of the series disappeared from observation after leaving the hospital, hence no experimental studies were made

Since publication of the report mentioned, we have had an opportunity to study 6 additional patients who showed hemorrhagic phenomena following the therapeutic use of arsphenamine derivatives It appeared to us important to record our experimental studies on these patients, particularly those on 5 patients of the series who showed typical purpura haemorrhagica following the use of neoarsphenamine or of bismarsen but who had no apparent reaction following the intravenous injection of mapharsen

Since our 1936 report and up to the time of the present report (March 1939), we have found recorded only 3 instances of thrombopenic purpura following arsphenamine therapy In the Soviet Russian medical literature, Izhevskiy ² in 1936 reported 1 case in which the condition followed neoarsphenamine therapy In 1937, Marin and Tettamanti ³ reported 1 case in which it followed the fourth injection of 0.18

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From the Divisions of Medicine and Dermatology of the University of California Medical School

1 Falconer, E H, Epstein, N N, and Wever, G K Purpura Hemorrhagica Following the Administration of Neoarsphenamine, Arch Int Med **58** 495 (Sept) 1936

2 Izhevskiy, K M Hemorrhagic Purpura Following Arsphenamine Therapy, Klin med **14** 1053, 1936

3 Marin, J V, and Tettamanti, J C Hemorrhagic Purpura Due to Arsphenamine Therapy, Rev med del Rosario **27** 127 (Feb) 1937

Gm of sulfarsphenamine. In the Danish medical literature, Stigaard⁴ reported the case of a young man with thrombopenic purpura following prolonged treatment with neoarsphenamine.

The present report concerns studies on 5 patients, 2 with thrombopenia and purpura following intravenous injection of neoarsphenamine and 3 showing similar phenomena after intramuscular injections of bismarsen. Another patient is included in this study because she had a somewhat different type of reaction to the arsenicals, showing large ecchymotic areas in the skin but no thrombopenia following administration of bismarsen and neoarsphenamine. These studies have been carried out in the hope of obtaining data that would be helpful in elucidating the mechanism causing thrombopenia and purpuric hemorrhages in sensitive, or sensitized, persons after administration of the arsphenamines. We believe, from our experience, that the condition is of much more frequent occurrence than published reports in the literature would indicate. From the time we began these studies on our first observed case (in 1933) until the end of 1938, we have observed and studied 8 patients with typical purpura haemorrhagica following administration of some form of arsphenamine. Seven of these patients have been tested for tolerance to mapharsen, and none has shown any untoward reaction or any evidence of purpura haemorrhagica following therapy with mapharsen.

METHODS AND TECHNIC

Six patients constituted our material and were studied either in the hematologic clinic or in the University of California Hospital. Of these, 5 were women and 1 a man. All were referred from the syphilis clinic because of hemorrhagic phenomena following administration of arsphenamine derivatives. In 4 instances bismarsen was used, and in 2, neoarsphenamine. Blood counts were made with standardized apparatus. The estimations of hemoglobin were made with the Sahli hemoglobinometer (Osgood and Haskins modification⁵). By this method, 13.7 Gm of hemoglobin equals 100 per cent. The platelet counts were performed according to the Rees and Ecker⁶ technic. In these experiments, a count of from 200,000 to 600,000 platelets per cubic millimeter was considered to be within the normal range. Blood counts were made usually in the morning hours, between 9 and 11 a. m. Hematocrit readings were made with Wintrobe⁷ pipets. Capillary fragility was estimated by the Dalldorf⁸ method, and all readings were based on

4 Stigaard, A. Care of Thrombopenic Purpura After Arsphenamine Administration Cured by Blood Transfusion, *Ugeskr. f. læger* **99** 138 (Feb. 4) 1937.

5 Osgood, E. E., and Haskins, H. D. A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J. Biol. Chem.* **57** 107 (Aug.) 1923.

6 Rees, H. M., and Ecker, E. E. An Improved Method for Counting Blood Platelets, *J. A. M. A.* **80** 621 (March 3) 1923.

7 Wintrobe, M. M. Classification of the Anemias on the Basis of Differences in the Size and Hemoglobin Content of the Red Corpuscles, *Proc. Soc. Exper. Biol. & Med.* **27**:1071, 1930.

8 Dalldorf, G. A Sensitive Test for Subclinical Scurvy in Man, *Am. J. Dis. Child.* **46** 794 (Oct.) 1933.

application of negative pressure for one minute. Our method was to make daily platelet counts after the initial complete blood count made at the first examination of a patient during an attack. After the platelet count had returned to normal or to nearly the normal level, the patient was given a dose of neoarsphenamine (0.1 Gm or less) intravenously to reproduce the attack. After admin-

TABLE 1—*Excerpts from Case Histories*

Case, Sex, Age	Type of Arsphenamine Used	Number of Doses and Size of Each Dose	Degree of Reaction and Symptoms	Onset of Purpura Following Reaction	Distribution of Purpuric Lesions	Date Patients First Seen	Type of Syphilis and Complications
1 F 44	Neoarsphenamine Tryparamide	11 (0.6 Gm) 1 (0.45 Gm) 2 (3 Gm)	Severe, nausea, vomiting and collapse after neoarsphenamine	Few hours	General	March 18, 1936	Cerebrospinal syphilis, tabetic crisis, myocardial weakness (tabetic dementia paralytica)
2 M 66	Neoarsphenamine Arsphenamine Bismarsen	1 (0.9 Gm) 26 (0.6 Gm) 4 (0.45 Gm) 5 (0.2 Gm) 1 (0.4 Gm) 3 (0.1 Gm)	Moderately severe, nausea, headache and chills after bismarsen	Few hours	General	Oct 8, 1937, 60 hrs after reaction	Central nervous system syphilis arterio sclerosis (general)
3 F 45	Neoarsphenamine Mapharsen Bismarsen	18 (0.3 Gm) 9 (0.15 Gm) 2 (0.45 Gm) 2 (0.1 Gm) 2 (0.2 Gm) 1 (20 mg) 12 (0.1 Gm)	Severe, nausea, vomiting, headache and collapse after neoarsphenamine	24 hrs	Arms, chest and lower extremities	Nov 27, 1937, 1 week after reaction	Latent syphilis, aortitis aortic insufficiency
4 F 48	Neoarsphenamine Bismarsen	1 (0.45 Gm) 29 (0.2 Gm)	Severe, nausea, vomiting and chills after bismarsen	24 hrs	General	Oct 12, 1938, 24 hrs after reaction	Latent syphilis, obesity, hypochromic anemia
5 F 30	Neoarsphenamine Bismarsen Mapharsen	1 (0.45 Gm) 42 (0.2 Gm) 12 (0.15 Gm) 1 (20 mg) 3 (30 mg)	No general reaction, pain at site of injection purpura after bismarsen	6 hrs	Breasts and extremities	Sept 14, 1938, 24 hrs after reaction	Secondary syphilis
6 F 42	Neoarsphenamine Mapharsen Bismarsen	12 (?) 1 (0.2 Gm) 1 (20 mg) 2 (0.2 Gm)	Moderate, nausea, vomiting, quantitative reaction to several different arsphenamines	24 hrs	Eczy- motic areas on arms and lower extrem- ities	May 25, 1937	Latent syphilis

istration, platelet counts were made at intervals of fifteen, thirty, sixty and one hundred and twenty minutes, then daily or less often until the count had returned to normal. This procedure was repeated after administration of mapharsen, beginning with 10 or 20 mg. Usually more than one dose of mapharsen was used in testing the patient's sensitivity to this drug.

PROTOCOLS AND EXPERIMENTAL DATA

CASE 1—From the excerpt of the case history (table 1) it will be seen that the patient, a woman aged 44, was sensitive to neoarsphenamine.

TABLE 2—Platelet Counts and Other Data in Case 1

Date	Time After Injection	Red Blood Cells, Millions per Cu Mm	Hemoglobin, %	Hemoglobin, Gm	Platelets	White Blood Cells per Cu Mm	Polymorphonuclears	Filamented Poly- morphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Myelocytes	Metamyelocytes	Comment
12/18/36		4.66	86	12.04	300,000	6,000	58	50	8			28	13	1	2	After mapharsen (10 mg.)
12/21/36	15 min				320,000		64	58	6	2		26	6			
	30 min				290,000		70	54	16	2		15	10			
	45 min				330,000		60	54	6	2		34	4			
	60 min				430,000		56	44	12	2		26	16			
12/28/36		4.72	86	12.04	450,000	7,500	60	48	12	4		20	16			
1/ 4/37		4.70	86		440,000	7,150	62	40	23			24	14			
1/11/37	15 min	4.68	86		510,000	7,450	52	48	4	2	2	30	14			Before mapharsen (40 mg.)
	30 min				470,000		70	52	18	4		14	12			After
	45 min				330,000		86	64	22		1	12	2			
	60 min				520,000		78	64	14	2		13	6			
					540,000		58	38	20	3		30	8	1		
1/16/37		4.63	86		270,000	7,250	58	50	8	1	1	24	16			
1/21/37	15 min	4.50	86		290,000	6,200	50	48	2	2	2	16	30	4		Before neoarsphenamine (0.075 Gm.)
	30 min				50,000		56	28	28			36	4			After
	45 min				30,000		94	58	36			4	2			
	60 min				30,000		86	40	46	2		12				
	5 hrs	4.45			20,000		66	32	34	2	1	27	2		2	
					20,000	7,100	94	68	26			2		4		
1/22/37	30 hrs	4.49	86		30,000	7,450	72	64	8	4		18	6			Hematoerit
1/26/37		4.61	86		50,000	7,300	70	66	4			12	18			Red blood cells 4,900,000 hemoglobin 92% = 12.6 Gm
1/28/37		4.05	86		170,000	7,500	66	70	16	1		25	7			Vol coefficient (packed cells) 13 cc per 100 cc blood, normal, 45 to 46 cc
2/ 3/37		4.08	90	12.3	170,000	9,450	62	46	16	2		22	12	2		Mean corp vol = 87.75 cu microns average 57, minimum 80, maximum 94
2/ 9/37		4.04	90		610,000	12,250	68	40	18	6		14	12			Mean corp hem = 25.71 micromicrograms average 29%, minimum 27, maximum 32
2/16/37		4.03	92	12.6	460,000	8,450	72	54	18			18	10			Mean corp hem content 29.3% average 37%, minimum 33%, maximum 38%
2/23/37	30 min	5.70	94	12.8	230,000	7,900	44	34	10			42	14			Vol index, 0.953 normal, 0.95 to 1.05
		5.51	94		270,000	7,300	70	52	18	2		18	10			Color index, 0.938, normal, 0.93 to 1.10

She was next given intravenous injections of mapharsen to test her sensitivity to this arsphenamine derivative. On Dec 12, 1936, she received 10 mg of mapharsen. On Jan 11, 1937, she received a second dose of mapharsen (40 mg). The platelet counts immediately after the injections and at longer intervals are recorded in table 2. After these injections, she experienced no untoward symptoms, the platelet counts were not decreased significantly and no petechial hemorrhages appeared in the skin or mucous membranes.

On Jan 21, 1938, the patient was given an intravenous injection of neoarsphenamine (0.075 Gm) to determine, in a measure, her sensitivity to this drug. While the needle was in the vein and she was still receiving the injection, her face became flushed and a dark reddish hue spread over her face and neck, she complained of a "choking sensation." At the end of the injection the pulse was rapid (130 beats per minute), she became nauseated and vomited, the hands and feet were cold, and a "splitting headache" came on. The acute symptoms gradually subsided. Table 2 shows the rapid drop in the platelet count. On

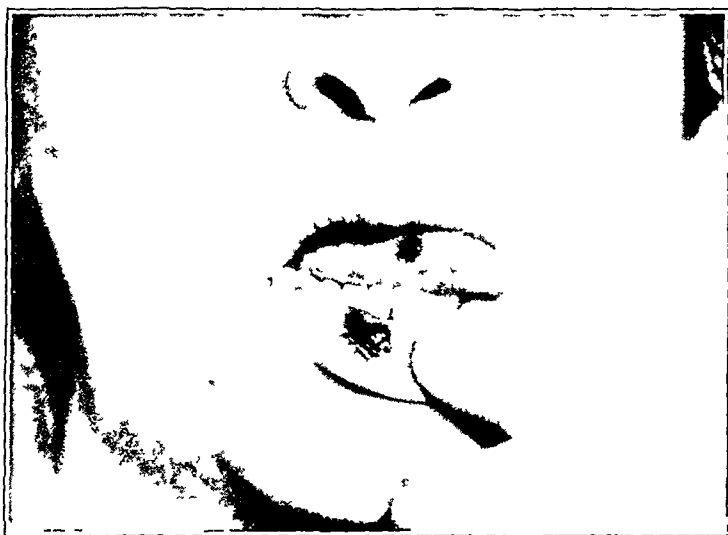


Fig 1—Hemorrhagic blebs appearing twenty-four hours after administration of 0.075 Gm of neoarsphenamine.

January 22, twenty-four hours after the injection, there were many small, dark red petechiae on the arms, chest and lower extremities. On the upper parts of both arms and over both ankles were ecchymotic areas from 6 to 8 cm in diameter. In the buccal mucosa on the right there was a hemorrhagic bleb about 2 cm in diameter, and there were three smaller areas (about 3 mm in diameter) in the buccal mucosa of the lower lip (fig 1). On this date she had a slight epistaxis, a small amount of uterine bleeding occurred and the urine showed many red blood cells in each microscopic field.

On February 23 intravenous injections of 40 mg of mapharsen were started and continued with short periods of rest until December 15. These treatments brought about freedom from her tabetic pains, and the platelet counts (tables 2 and 3) ranged between 160,000 and 300,000 per cubic millimeter. No untoward symptoms and no purpuric or other hemorrhages occurred during her many injections of mapharsen.

CASE 2—A man aged 66, had a reaction from bismarsen on Oct 7, 1937 (table 1). By October 9 the platelet count had risen to 240,000 per cubic millimeter. On October 12 the platelet count was 360,000. At this time the patient

TABLE 3—Further Platelet Counts and Miscellaneous Data in Case 1

Date	Time After Injection	Red Blood Cells, Mm	Hemoglobin, %	Hemoglobin, Gm	Platelets	White Blood Cells Per Cu Mm	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Myelocytes	Metamyelocytes	Comment
3/ 1/37		5.52	94		310,000	7,250	58	42	16	4		22	14		2	
3/ 8/37		5.57	96	13.2	230,000	7,900	60	44	16	2		20	18			
3/15/37		5.51	94	12.8	270,000	8,100	69	52	17	1		14	16			
3 23/37		5.48	94		260,000	8,350	70	62	8	6		12	12			
3/29/37		5.66	94		200,000	8,600	80	54	26			14	6			
4/ 5/37		5.61	94		220,000	7,400	66	38	28	2	1	12	16	1	2	
4/19/37		5.54	94		180,000	9,100	61	45	16		1	14	22		2	
5/10/37		5.42	96	13.2	220,000	8,800	73	61	12			22	4	1		
5/24/37		5.48	94	12.8	200,000	9,400	58	38	20	4		14	24			
6/28/37		5.63	94		220,000	7,700	53	43	15	6		23	13			Before mapharsen (40 mg)
	20 min				230,000		56	43	13	6		28	16			After
	60 min				180,000	6,100	52	34	18	4		34	10			
7/ 6/37		5.67	94		160,000	9,700	58	46	12			26	16			
	20 min				190,000		56	46	10	6		20	18			
7/12/37		5.80	94		170,000	10,050	70	48	22	2		19	9			Before mapharsen (40 mg)
	30 min				180,030		70	56	14	3	3	22	2			After
7/19/37		5.72	96	13.2	240,000	9,000	58	42	16	2		18	22			Before mapharsen (40 mg)
	30 min				220,000	9,700	74	60	14	2		13	11			After
7/26/37		5.76	93		210,000	7,600	68	50	18			18	14			Before mapharsen (40 mg)
	30 min				220,000	8,100	66	52	14	1	1	22	18			After
8 / 2/37		5.70	100	13.8	270,000	8,600	68	52	16	4		22	6			Before mapharsen (40 mg)
	30 min				240,000	9,100	56	40	16	2		22	20			After
8/ 9/37		5.59	98	13.4	190,000	7,400	60	40	20	2		20	18			Before mapharsen (40 mg)
	30 min				190,030	7,650	50	23	22	6	1	30	13			After
8/16/37		5.58	98		170,000	7,700	78	64	14			12	10			Before mapharsen (40 mg)
	30 min				190,030	7,950	56	39	17	1		25	15			After
8 23/37		5.74	98		210,000	8,150	66	43	23	2		16	16			
11/15/37		5.60	100	13.8	290,000	7,100	66	55	11			26	8			Before mapharsen (40 mg)
	15 min				310,000		52	42	10	1	1	26	20			After
11/22/37		5.47	100		290,000	6,300	38	30	8	2		32	28			

TABLE 4 —Platelet Counts and Other Data in Case 2

Date	Time After Injection	Red Blood Cells, Millions per Cu Mm	Hemoglobin, %	Hemoglobin, Gm	Platelets	White Blood Cells per Cu Mm	Polymorphonuclears	Filamented Poly- morphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Comment
10/ 8/37		5.58	104	14.25	160,000	14,300	69	61	8	2	1	20	8	
10/ 9/37		5.60	104		240,000	10,200	78	76	2	1		13	8	
10/12/37	15 min				360,000		75	73	2	2		12	11	Before 6 mg mapharsen
	30 min				300,000		77	63	12	1	1	11	10	After
	60 min				350,000		62	56	6	2		20	10	
	90 min				370,000		62	56	6			18	20	
					350,000		52	40	12	2		32	16	
10/13/37		5.51	104		360,000	9,700	55	46	9	1		27	17	
10/16/37	15 min	5.46	104		540,000	12,700	66	45	21	4		18	12	Before 30 mg mapharsen
	30 min				560,000		75	50	23	2		15	15	After
	60 min				430,000		70	49	21			20	10	
					530,000		65	47	18	5		15	15	
10/18/37		5.56	104		480,000	11,600	59	45	14	3		24	14	
10/21/37	15 min	5.68	104		580,000	12,400	62	54	8	4		24	10	Before 0.015 Gm neoparsphenamine
	30 min				250,000	11,000	68	60	8	4		20	8	After
	60 min				80,000	8,500	62	54	8	2		32	4	Hicnatocrit
	2 hrs				150,000	10,100	76	65	11	2		20	2	Packed cell vol, 39, normal, 45.46
	3 hrs				170,000	13,900	77	57	20	1		20	2	Mean corp vol, 78, normal, 87
	7 hrs				110,000	21,000	82	52	30	2		12	4	Mean corp hgb, 28, normal, 29.5
					190,000	14,800	69	58	11	5		22	4	Mean corp hgb concent, 35.9, normal, 35
10/22/37		5.50	102	13.97	100,000	12,600	72	60	12	4		19	5	Vol index, 0.899, normal, 0.95-1.05
10/23/37					130,000	8,000	68	58	10	4		22	6	Color index, 0.949, normal, 0.90-1.10
10/25/37		5.53	102		300,000	7,200	62	52	10	3		29	6	Saturation index, 1.057, normal, 0.87-1.23
10/26/37		5.58	102		470,000	12,400	70	56	14	2		21	7	Icteric index, 2, normal, 4.7
10/28/37		5.40	102		300,000	15,100	78	64	14	3		16	3	—20 cm pressure 20.30 petechiae —15 cm pressure, 7.9 petechiae
11/ 4/37		5.43	102		410,000	15,300	65	55	10	5		23	7	—10 cm pressure none
														—15 cm pressure, 3 petechiae —20 cm pressure, 7 petechiae

was given 6 mg of mapharsen intravenously in order to determine whether he was sensitive to this drug. We knew that he was sensitive to neoarsphenamine, because he had a history of a severe reaction in 1929 following the taking of 0.45 Gm of this drug, which had made it necessary for him to enter the University Hospital for two days. After the injection of mapharsen the platelet count fluctuated slightly, but at the end of one and one-half hours it was at about the same level as before the injection (table 4). There were no clinical signs or symptoms of a reaction.

On October 21 the Dalldorf capillary fragility test showed

—25 cm pressure	8 to 10 petechiae
—20 cm pressure	3 to 5 petechiae
—15 cm pressure	no petechiae

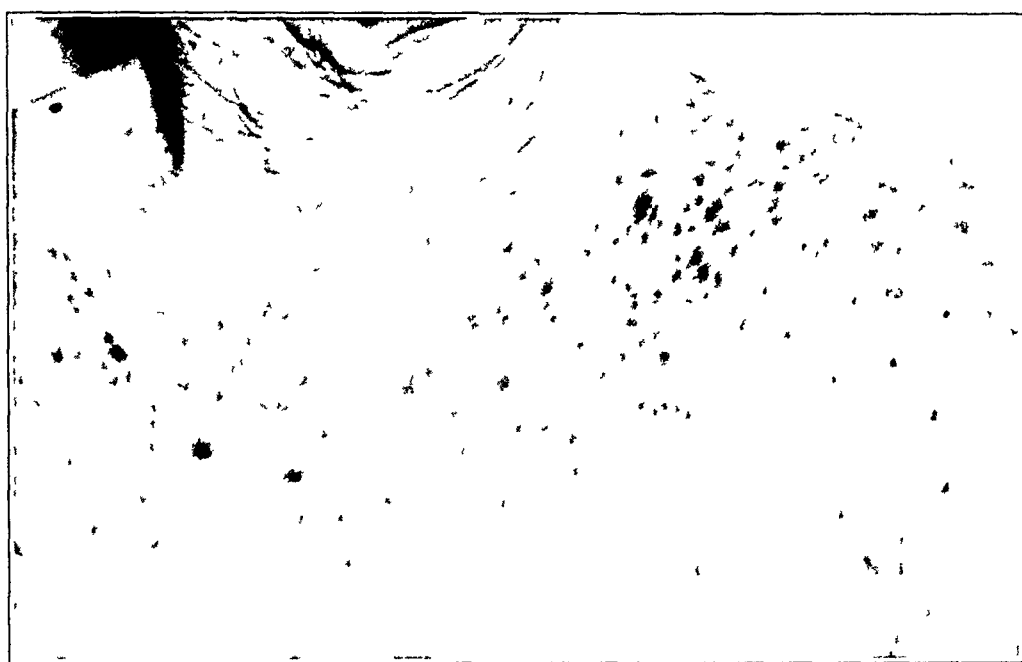


Fig 2—Purpuric lesions which appeared two hours after injection of 0.015 Gm of neoarsphenamine

These tests were done at 9 a. m., and at 9:30 a. m. 0.015 Gm of neoarsphenamine was administered intravenously. Immediately afterward, the patient complained of nausea and became cyanotic, the pulse was rapid, and he felt faint. The blood pressure dropped from 120 mm of mercury systolic and 80 diastolic to 85 systolic and 60 diastolic. Thirty minutes after the injection the platelet count was 80,000 per cubic millimeter. At this time the Dalldorf capillary fragility test showed

—15 cm pressure	a shower of petechiae
—10 cm pressure	20 to 25 petechiae

Two hours after the injection, purpuric spots appeared on the upper anterior surface of the chest, on the arms and below the knees (fig 2). At this time the patient had a chill, for which 1 cc of epinephrine hydrochloride (1:1,000) was administered subcutaneously. The platelet count rose to 170,000 per cubic millimeter. The patient was transferred from the clinic to the hospital. Seven hours after the injection and just after a hot tub bath, the platelet count was 190,000.

per cubic millimeter On October 22, twenty-four hours after the injection, the Dalldorf capillary fragility test showed

— 15 cm pressure	a shower of petechiae
— 10 cm pressure	30 petechiae

On October 23, the test showed

— 20 cm pressure	40 to 50 petechiae
— 15 cm pressure	30 to 35 petechiae
— 10 cm pressure	12 to 20 petechiae

On October 25, the platelet count was 300,000, and the test showed

— 20 cm pressure	20 to 30 petechiae
— 10 cm pressure	7 to 9 petechiae

On November 4, the platelet count was 410,000, and the test showed

— 20 cm pressure	7 petechiae
— 15 cm pressure	3 petechiae
— 10 cm pressure	no petechiae noted

CASE 3—On Nov 29, 1937, a woman aged 45 who was known to be sensitive to neoarsphenamine (table 1) was tested with 20 mg of mapharsen administered intravenously The platelet count rose immediately after this injection (table 5), no untoward symptoms occurred On December 3 she received 0.1 Gm of neoarsphenamine intravenously While still receiving the injection, she began to complain of nausea As soon as the injection was finished, vomiting occurred, the pulse became rapid and feeble, the hands and feet were cold and a severe headache came on Two hours after the injection, petechiae appeared on the upper parts of both arms and on both lower extremities below the knees At the end of thirty minutes after the injection, the platelet count was 80,000 per cubic millimeter, sixty minutes after the injection, the count was 130,000, one hundred and twenty minutes after the injection, the count was 190,000 On the following day the platelet count was 70,000 per cubic millimeter This was the first time we had observed a temporary rise in the platelet count following administration of neoarsphenamine to a patient known to be sensitive to this drug and to have previously exhibited purpura haemorrhagica following its intravenous use

CASE 4—On Oct 10, 1938, after an intramuscular injection of 0.2 Gm of bismarsen, the patient, a woman aged 48, had a severe reaction, the thrombocytes dropping as low as 50,000 per cubic millimeter By October 17 the platelet count had risen to 310,000 In order to test her sensitivity, we gave her on this date 20 mg of mapharsen intravenously The platelet count was not lowered by this drug (table 6), and no reaction of any type was noted after the injection

When she was first seen in the hematologic clinic we noted the presence of hypochromic anemia, and she was given intramuscular injections of concentrated liver extract (Lilly) with ferrous sulfate (0.23 Gm, four doses daily) In addition to its possible effect on the hemopoietic system, we desired to ascertain whether liver extract exercises an ameliorating effect on the toxic reaction occurring after administration of the arsphenamine to a patient sensitive to at least one of these preparations, the sulfarsphenamine or bismarsen On both November 22 and November 29 she was tested further with 40 mg of mapharsen No significant change in the platelet counts occurred, and she showed no evidence of reaction On December 14, 0.1 Gm of neoarsphenamine was administered intravenously The platelet count dropped slightly (table 6), but there were

TABLE 5—Platelet Counts and Other Data in Case 3

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm	Hemoglobin, %	Hemoglobin, Gm	Platelets	White Blood Cells per Cu. Mm	Polymorphonuclears	Rilamented Poly- morphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Metamycytes	Comment
11/27/37		5.60	104	14.25	200,000	10,300	68	54	14	6		14	12		7 days after neorarsphenamine (0.2 Gm.) and purpura haemorrhagica
11/29/37	15 min				210,000	11,400	80	75	5			16	4		Before mapharsen (20 mg.)
	30 min				280,000	9,900	66	70	16	1	1	30	2		
	60 min				260,000	10,300	79	73	16	3		12	6		
	120 min				310,000		52	30	20	3	1	40	4		
12/ 3/37		5.41	101	14.25	270,000	8,500	82	57	25	4		9	4	1	Before neorarsphenamine (0.1 Gm.)
	15 min				160,000	6,200	78	57	21	2		15	3	2	In occasional very large platelet all others very small in count
	0 min				80,000	7,600	90	68	22	2		8			ing chamber
	60 min				130,000	8,100	84	74	10	1		13	2		
	120 min				190,000	9,150	76	53	23	5		19			
12/ 4/37					70,000	11,200	72	61	8	6		18	4		
12/ 9/37		5.44	104		140,000	9,800	69	60	9	2		21	8		
12/ 7/37		5.77	104		240,000	11,400	58	40	18	2		32	9		
12/ 8/37		5.70	104		270,000	10,000	62	70	12	4		22	12		
12/ 6/37		5.76	104		250,000	9,100	70	56	14			26	4		
12/10/37		5.89	104		350,000	12,900	72	64	8	3		32	3		
12/11/37		6.01	104		370,000	8,800	66	50	16	2		18	14		
12/11/37		6.03	104		550,000	9,700	70	76	14	3		19	8		
12/21/37		5.97	104		510,000	10,600	62	50	12	5		29	4		
12 29/37		5.84	104		480,000	12,300	82	64	22			16	2		
1/ 3/38		5.80	104		400,000	9,600	72	60	12	4		21	3		

TABLE 6—Platelet Counts and Other Data in Case 4

Date	Time After Injection	Red Blood Cells, Millions per Cu Mm	Hemoglobin, %	Hemoglobin, Gm	Platelets	White Blood Cells per Cu Mm	Polymorphonuclears	Filamented Poly- morphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Comment
10/11/38		5.50	66	9.0	70,000 70,000	8,900	60	49	11	2		20	18	
10/12/38		5.30	66		50,000	8,100	74	62	12	2		12	12	
10/13/38		4.97	64	8.77	100,000	9,400	69	60	9	1	1	16	12	
10/14/38		4.80	64		130,000	9,800	65	52	13	2	2	18	13	
10/15/38		4.62	62	8.49	140,000	10,000	62	52	10	1	1	25	11	
10/17/38		4.71	64	8.77	310,000 330,000 330,000 330,000 350,000 310,000	11,000 13,600 12,900 12,600 11,900	69 72 70 73 69	59 63 48 55 51	10 9 22 18 18	3 2 3 2 1	1	15 16 20 11 20	12 10 7 14 10	Before 20 mg mapharsen After
10/18/38	15 min	4.68	62	8.49	320,000	11,800	66	53	13		1	21	12	
10/20/38		4.60	62		340,000	13,400	66	52	14	2		18	14	
10/22/38		4.57	62		590,000	13,800	72	60	12	1	1	11	12	
10/25/38		4.63	60	8.22	570,000	10,050	70	61	6	2	2	18	8	
10/27/38		4.60	60		410,000	11,800	70	62	8	2		12	16	
11/14/38		4.80	58	7.95	590,000	14,000	65	55	10	2		17	16	
11/18/38		4.87	64	8.77	690,000	14,300								
11/22/38	15 min	4.90	62	8.49	680,000	15,700	66	52	14	3	1	20	10	Before 40 mg mapharsen After
	30 min				880,000	15,400	61	50	11	1		23	12	
	60 min				760,000	12,800	69	54	15	2		18	11	
	2 hrs				690,000	14,900	70	50	20			10	20	
					670,000	15,200	71	60	11	3	1	10	15	
11/29/38	15 min	5.10	80	10.96	430,000	13,100	67	65	2	3		16	14	Before 40 mg mapharsen After
	30 min				460,000	14,300	66	58	8	2		18	14	
	60 min				470,000	13,800								
					450,000	13,700	70	56	11	3	1	18	8	
12/ 5/38		5.04	76	10.41	710,000	18,300	74	60	11			12	11	
12/14/38		5.02	70	9.59	540,000	9,300	80	76	1	1	1	10	8	Before 0.1 Gm neocarsphenamine After
	15 min				510,000	9,600	79	68	11	1		12	8	
	30 min				510,000	8,600	84	71	10			16	6	
	60 min				480,000	12,100	78	69	9			10	6	
	90 min				490,000	11,300	83	77	6	1		10	6	

Lilly's sol liver ext conc 3 cc intramuscularly twice per week

TABLE 7—Further Platelet Counts and Miscellaneous Data in Case 4

Date	Time After Injection	Red Blood Cells, Millions per Cu Mm	Hemoglobin, %	Hemoglobin, Gm	Platelets	White Blood Cells per Cu Mm	Polymorphonuclears	Flamemted Poly- morphonuclears	Nonflamemted Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Myelocytes	Metamyelocytes	Comment
12/21/38	15 min	5.05	89	9.32	420,000	10,700	74	59	15	1		15	10			Before 0.1 Gm neorsphenamine After
	30 min				490,000	11,800	69	63	6	1		18	12			
	60 min				620,000	11,300	72	67	5	1		16	11			
	90 min				590,000	12,100	72	66	6			18	10			
12/22/38					500,000	11,900	72	68	4	1		15	12			
					480,000	11,800	73	59	14	1		14	12			
		5.16	65	9.04	570,000	9,200	72	64	8	4		14	10			Before 0.1 Gm bismarsen After
	15 min				510,000	7,800	72	63	9	2	1	14	11			
12/30/38	30 min				460,000	16,300	76	63	13			15	7	1		
	60 min				300,000	12,100	82	52	30	2		10	6			
	90 min				210,000	9,300	87	57	30			8	5			Epinephrine, 1 cc (1:1,000)
	2 hrs				320,000	9,100	85	59	35	2	1	5	7			
12/31/38 a m p m	3 hrs				170,000	8,400	84	51	33	2	1	6	7			
		5.14	64	8.77	60,000	11,500	70	54	16	1	1	12	16			
					80,000	12,100	78	64	14	3		10	9			
		4.83	60	8.22	110,000	15,750	74	62	12	4	1	12	9			
1/ 3/39		4.88	60		160,000	19,100	70	60	10	4	2	12	12			
1/ 4/39					320,000	17,300	70	63	7	3	4	9	14			
1/ 5/39		5.41	62	8.49	560,000	13,400	66	65	1	2		18	14			Before 0.1 Gm sulfarsphenamine After
2/20/39	15 min				30,000	12,900	61	12	49			28	8		3	
	60 min				20,000	11,700	92	38	54			6	2		1	
	3 hrs				25,000	15,100	84	29	55	1		10	9			
	8 hrs	5.51	62		50,000	16,300	88	44	44			8	4			
2/21/39		4.72	56	7.67	80,000	14,000	88	36	52			8	4			
		4.74	54	7.40	80,000	10,300	82	62	20			7	11			
	2/22/39 a m p m	4.70	54		90,000	11,400	85	65	20			6	7			
		4.38	50	6.85	120,000	13,000	88	67	21			7	5			
2/23/39 a m p m		4.31	50		100,000	13,600	82	62	20			7	11			
2/24/39 a m p m		4.29	50		110,000	9,300	79	60	19	1		9	11			
		4.33	50		100,000	10,500	82	68	14	3		10	5			
		4.41	52	7.12	240,000	13,600	82	72	10	2		13	3			
	2/25/39	4.30	54	7.4	150,000	21,000	72	63	9	3		16	9			
2/26/39		4.33	56	7.67	140,000	22,700	71	54	20	4		12	10			
3/ 1/39		4.41	56		300,000	18,900	72	59	13			18	10			
3/ 2/39		4.50	60	8.22	410,000	12,300	70	62	8	1		21	8			
3/11/39																

Hematocrit
 Picked cell volume 33 normal average, 45.46
 Mean corpuscular volume, 73.3 normal, 87
 Mean corpuscular hemoglobin, 1.83, normal, 2.95
 Mean corpuscular hemoglobin conc. 24.9, normal 35
 Volume index, 0.84 normal, 0.95105
 Color index, 0.62, normal, 0.90110
 Saturation index, 0.74, normal, 0.87123

no untoward symptoms following the injection. On December 21 a second intravenous injection of neoarsphenamine (0.1 Gm.) was given. The platelet count gradually rose after the injection. On the next day the number of platelets was still above the level of the count made just before the neoarsphenamine was administered (table 7). No reaction of any sort was observed from this second dose. We decided to test her sensitivity to bismarsen, accordingly, on December 30, she received an intramuscular injection of 0.1 Gm. of bismarsen in the left buttock. The platelet count before the injection was 570,000 per cubic millimeter, ninety minutes after the injection it dropped to 210,000. The patient became nauseated and was pale, the pulse was rapid and weak, and the hands and feet were cold immediately after the injection. Ninety minutes after the bismarsen was given, a chill came on, and, as the pulse was rapid and weak, she was given 1 cc. of epinephrine hydrochloride (1:1,000) subcutaneously. The platelet count rose immediately and two hours after the injection it was 320,000 per cubic millimeter. On the following day, December 31, the platelet count was 60,000, and a purpuric eruption had appeared on the anterior surface of the chest, the abdomen, both arms and the lower extremities. On Feb. 20, 1939, fifty-two days after the injection of bismarsen, the patient was tested to determine her sensitivity to sulfarsphenamine. After a preliminary intramuscular injection of 3 cc. of Lilly's concentrated liver extract, 0.1 Gm. of sulfarsphenamine was slowly injected intravenously. When the last portion of the solution was entering the vein the patient became cyanotic, said that her head felt very peculiar and without further warning fell forward, collapsing in her chair. Because of her obesity she had been allowed to sit in a chair while receiving the injection. She was stretched out immediately on the floor, and artificial respiration was employed, as her body had become rigid and respirations had ceased. One cubic centimeter of epinephrine hydrochloride (1:1,000 solution) was administered subcutaneously. The pulse was feeble but slow. Under artificial respiration she began to breathe again, and after two or three minutes the rigidity of her body disappeared and she became conscious, asking what had happened. A second dose of 1 cc. of epinephrine hydrochloride (1:1,000 solution) was given. Twenty minutes after the injection the platelet count was 30,000 per cubic millimeter, and purpuric areas from 1 to 3 mm. in diameter began to appear on the neck, the upper anterior surface of the chest and the arms. She began to expectorate blood-tinged mucus, and her lungs became filled with coarse, moist rales. She was admitted at once to the University of California Hospital and placed in an oxygen tent, as it was evident that pulmonary edema had supervened. The development of mild bronchopneumonia necessitated a stay of eleven days in the hospital, but she made an uneventful recovery.

CASE 5—The patient was a Negress aged 30. On Sept. 13, 1938, about three and one-half hours after the fifty-fourth intramuscular injection of bismarsen in a dose of 0.2 Gm., she began to expectorate blood-tinged saliva. No obvious reaction to the injection of bismarsen occurred except pain at the site of injection. She expectorated considerable blood during the night following her treatment, and on the next day, September 14, there were many small petechiae on her chest and extremities (fig. 3). She reported to the syphilis clinic on this date and was admitted to the hospital, since by this time bleeding from the gingival margins had appeared. A few hours after she entered the hospital, the blood pressure in millimeters of mercury dropped from 130 systolic and 80 diastolic to 100 systolic and 60 diastolic. At entry, the bleeding time (Duke) was fifteen minutes, the blood clot showed no retraction after forty-eight hours. At this time the platelet count was 30,000 per cubic millimeter (table 8). After entry the patient stated that for ten years she had been addicted to the use of morphine. Between

September 16 and September 19 (the date of discharge from the hospital), she received one hypodermic injection of morphine sulfate of 0.01 Gm and thirteen hypodermic injections of morphine sulfate of 0.03 Gm each.

A biopsy of the sternal marrow was performed by Dr. Stacy R. Mettier on September 16. Bleeding from the gums had ceased by September 15. On September 17 the patient received an intravenous injection of 10 mg of mapharsen. By September 19, the platelet count had risen to 300,000 per cubic millimeter, the patient felt well and, at her request, was discharged from the hospital.

She returned to the hematologic clinic on October 4 and was given an intravenous injection of 15 mg of mapharsen (table 8). On October 18 she received 0.1 Gm of neoarsphenamine intravenously (see table 8 for results). While in the hospital, she had been tested for sensitivity to mapharsen, and she was tested again shortly after discharge. This last injection was to ascertain whether she was sensitive to neoarsphenamine. There were no untoward subjective symptoms of

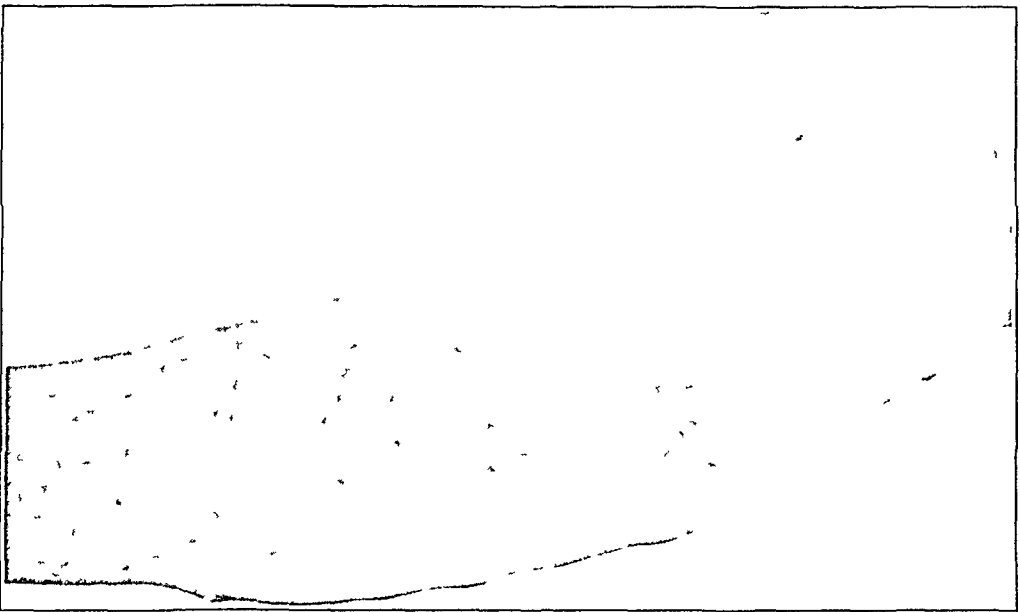


Fig. 3—Closely packed petechiae on the arm twenty-four hours after administration of bismarsen.

any kind during or after this injection of neoarsphenamine, but the number of platelets decreased rapidly, and four hours after the injection the bleeding time was thirty-five minutes. The blood clot showed no retraction after twenty-four hours.

CASE 6—After a series of twelve intravenous injections in Chicago in 1929, a woman aged 42 could not tolerate further treatment with neoarsphenamine without onset of nausea, vomiting and malaise. The drug injected in 1929 was presumably neoarsphenamine, but we have only the patient's opinion concerning its identity. During October 1935, after intravenous injection of 20 mg of mapharsen, nausea and vomiting occurred. Between October 1935 and July 1936, she received twenty-six intramuscular injections of bismarsen (0.2 Gm each), with no apparent reactions and no hemorrhagic phenomena. On April 30, 1937, after intravenous injection of 0.2 Gm, she immediately had symptoms of nausea and vomiting. During May 1937 she received two intramuscular injections, each of 0.2 Gm of bismarsen. After each injection large ecchymotic areas appeared

TABLE 8—Platelet Counts and Other Data in Case 5

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm	Hemoglobin, %	Hemoglobin, Gm	Platelets	White Blood Cells per Cu. Mm	Polymorphonuclears	Filamented Poly- morphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Comment
9/14/38	Noon	4.70	96	13.15	30,000	12,200	50	48	2	1	1	30	18	Count during first reaction to 0.2 Gm bismarsen 9/16/38, sternal biopsy
	6 p m				30,000	12,300	73	70	3			19		Myeloblasts, 6
	8 p m				50,000	12,400	81	71	10	1	1	11	6	
9/15/38	8 a m	4.76	96		80,000	12,400	76	66	10	4		16	4	Myelocytes neutrophils 13, eosinophils 2
	12 noon				70,000	12,600	68	58	10	1		20	11	Metamyelocytes neutrophils 17, eosinophils 2
	4 p m				80,000	11,800	61	50	11			27	12	Polymorphonuclears neutrophils 24, eosinophil 1
	6 p m				100,000	9,900	54	42	12			30	16	Lymphocytes, 7
9/16/38	8 a m	4.68	96		70,000	8,700	74	66	8	2		18	6	Megakaryocytes, 0
	12 noon				90,000	8,900	75	69	6	4		17	4	Megaloblasts, 6
	5 p m				100,000	8,600	63	60	8	2	2	18	10	Normoblasts, 23
9/17/38	8 a m	4.74	96		200,000	7,400	76	64	12	1	1	14	8	Before 10 mg mapharsen
	2 hrs				240,000	8,300	75	67	8	1	1	13	10	After
	4 hrs				260,000	8,850	73	71	2	1	1	13	12	
	6 hrs				270,000	8,350	75	70	5	2		15	8	
9/18/38	8 a m	4.78			270,000	8,600	73	70	3	1	1	15	10	
	5 p m				290,000	9,100	62	58	4	1		21	16	
9/19/38		4.80	96		300,000	9,300	60	60	6	2		21	11	
10/ 4/38	15 min	4.60	90	12.33	340,000	11,200	60	60	10	3		19	8	Before 15 mg mapharsen
	30 min				410,000	9,100	56	52	8	1		30	9	After
	60 min				390,000	9,900	60	52	8			27	12	
	2 hrs				420,000	9,700	53	48	10	6		27	15	
10/18/38	15 min	4.82	88	12.06	400,000	9,700	62	52	10	4	1	23	10	Before 0.1 Gm neoarsphenamine
	30 min				380,000	9,800	58	48	10	1	1	33	7	After
	60 min				200,000	8,900	66	55	11	2	1	27	4	
	1 1/4 hrs				110,000	8,500	80	68	12	1		15	4	Hematoerit
	4 hrs				65,000	8,600	72	60	12	2		18	8	Packed cell volume, .40, normal average, .45 .46
10/19/38		4.72			48,000	8,700	77	65	12	4	1	12	6	Mean corpuscular volume, 78.5, normal, 87
					40,000	8,800	74	58	16	2	1	17	6	Mean corpuscular hemoglobin, 24.7, normal, 29.5
10/20/38		4.80	90	12.33	100,000	9,100	54	48	6			23	18	Mean corpuscular hemoglobin concentration, 31.5, normal, 35
10/25/38		4.71	88	12.06	270,000	8,800	50	42	8	6		37	7	Volume index, 0.90, normal, 0.95 .1.05
					340,000	9,000	50	44	6	1	1	36	12	Color index, 0.84, normal, 0.90 .1.10
														Saturation index, 0.93, normal, 0.87 .1.23
														Icteric index, 5, normal, 4.7

TABLE 9—Platelet Counts and Other Data in Case 6

Date	Time After Injection	Red Blood Cells, Millions per Cu Vmm	Hemoglobin %	Hemoglobin, Gm	Platelets	White Blood Cells per Cu Mm	Polymorphonuclears	Filamented Poly- morphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Before 0.1 Gm After	neoarsphenamine	Comment
5/25/37	15 min	5.07	18	11.51	100,000	11,700	46	36	10	1	1	30	22			
	30 min				210,000		68	59	7	2	1	25	6			
	45 min				110,000		68	54	11	3		28	4			
	60 min				120,000		71	61	10			23	6			
					120,000		67	60	4	3		23	7			
5/26/37		5.01	13		100,000	11,600	54	36	18			32	14			
5/27/37		5.45	84		120,000	10,900	56	35	21	2	1	32	9			
5/28/37		5.03	81		150,000	9,600	40	24	16	1		43	16			

on the arms and lower extremities. On May 25 when this patient presented herself for study of the type of reactions she exhibited after treatment with the arsphenamines, she was given a test dose of 0.1 Gm of neoarsphenamine intravenously. No untoward symptoms followed this injection. The platelet count rose immediately after the injection (table 9). In twenty-four hours it had returned to the level of the count before the injection (100,000 per cubic millimeter). No late toxic symptoms appeared, but twenty-four hours after administration of 0.1 Gm of neoarsphenamine, two ecchymotic areas about 3 cm in diameter appeared at the site of the injection into the vein, and over the internal condyle of the right knee there was an ecchymotic area 5 by 4 cm. Results of the Dalldorf capillary fragility test were as follows:

Before injection of neoarsphenamine April 30

—25 cm pressure	4 petechiae
—20 cm pressure	4 petechiae

Two hours after injection

—25 cm pressure	4 petechiae
—15 cm pressure	3 petechiae

Twenty-four hours after injection

—30 cm pressure	6 petechiae
—25 cm pressure	3 petechiae
—20 cm pressure	3 petechiae
—15 cm pressure	no petechiae

ANALYSIS OF DATA AND COMMENT

Analysis of Case 1—The data show that the patient had become very sensitive to neoarsphenamine after eleven injections of 0.6 Gm each and one of 0.45 Gm. Later, when she was given an intravenous injection of neoarsphenamine of as small an amount as 0.075 Gm she showed an immediate reaction characterized by circulatory collapse and stasis indicative of shock. The rapidity with which the symptoms appeared after the injection was begun suggested a toxic action on the vasomotor centers, in fact, it appeared as if the stage had been previously set for a reaction to occur, so prompt was the response. In contrast to this reaction was the absence of any observable reaction following intravenous injections of mapharsen, of which the patient received some twenty-three while under our observation, the doses varying from 20 to 40 mg. She also received six intravenous injections of tryparsamide, 0.6 Gm each, without reaction, but after the seventh injection (of 0.6 Gm) a reaction occurred in the form of pains in the extremities, edema of the lower extremities, nausea and vomiting. Unfortunately she was not sent to us at this time for study, and we do not know whether the platelet count had decreased. No purpuric manifestations appeared.

Analysis of Case 2—Analysis of the patient's reaction to bismarsen shows that it came on within a few hours after the injection and was characterized by nausea, headache and chills. The longer period in

the development of his reaction may have been due to the fact that this drug was administered intramuscularly. It should be noted that he was very sensitive to neoarsphenamine also. After injection of 0.015 Gm intravenously, he exhibited mild but prompt symptoms of shock. The results of the Dalldorf capillary fragility test were normal before the injection of neoarsphenamine but paralleled the immediate rapid drop in the platelet count and the subsequent rise following the twenty-four hour interval after injection. A significant feature in connection with these data is the considerable increase in the platelet counts following the subcutaneous injection of 1 cc of 1:1,000 epinephrine and the hot bath given seven hours after the administration of 0.015 Gm of neoarsphenamine. It seems apparent that these measures increased the circulatory tone by contracting the capillary bed and restored to the general circulation platelets that were temporarily out of circulation. It seems probable that in instances of this type the dilated capillary bed allows diffusion of blood into the skin, resulting directly in the small hemorrhages constituting the purpura haemorrhagica. The greater portion of platelets may pass out from the arterial circulation into the capillaries but are unable to prevent diffusion of blood from the capillaries.

Analysis of Case 3—The patient in this case was the third of this series to exhibit phenomena of shock following administration of a test dose of neoarsphenamine. She was a "cardiac invalid" and therefore was not a fit subject for reproducing neoarsphenamine reactions. For this reason our experimental procedures with her were limited. She did not show any reaction to 20 mg of mapharsen given intravenously. After the test dose of neoarsphenamine (0.1 Gm) the platelet count dropped rapidly, but one hour after the injection the platelet count began to rise, and two hours after the injection the count was 190,000 per cubic millimeter (more than double the number of platelets fifteen minutes after the injection). This was the only time we have noted a rise of platelets following reaction from an arsenical once the count had begun to fall, except as has been noted (when epinephrine had been administered or other procedures used).

Analysis of Case 4—Two interesting and important features deserve special mention in the analysis of our data on case 4. The patient was very sensitive to bismarsen, having received some twenty-nine injections before we began our studies. She did not appear to be sensitive to neoarsphenamine. Her history indicated that she had received only one previous dose (0.45 Gm given intravenously), after which there had been no reaction. We gave her two intravenous injections of neoarsphenamine of 0.1 Gm each. There was no reaction and no significant drop in the platelet count. The absence of a reaction and of any untoward symptoms following administration of neoarsphenamine might

be ascribed to the protective action of her previous intramuscular injections of liver extract. If this were true, we should expect some degree of similar protection against the toxic systemic effects of bismarsen and sulfarsphenamine. Her reactions to these two substances were strong evidence against any protective value of parenterally administered liver extract in ameliorating the toxic effects of the arsphenamines. In respect to the platelet counts after injection of sulfarsphenamine, table 5 B shows that no rise occurred after two subcutaneous injections of 1 cc of epinephrine hydrochloride (1:1,000 solution), such as we noted in case 2. An explanation that seems quite probable is that the patient's tissues were unable to absorb the epinephrine owing to extreme shock, with the accompanying feeble circulation and capillary stasis.

Analysis of Case 5—In the data on case 5, it is important to note that this patient had received some fifty-three injections of bismarsen (0.2 Gm each) before purpura followed its use. When she did finally become sensitized to bismarsen, she failed to have the severe constitutional symptoms usually seen. The same facts apply to her sensitivity to neoarsphenamine. We believe she had systemic reactions as well as thrombopenic purpura but the reaction was probably modified by her addiction to a drug (morphine). The fall of blood pressure occurring the first two hours after hospitalization accompanied by a platelet count of 30,000 per cubic millimeter suggests a constitutional reaction.

A sternal biopsy (button type) was performed while the patient was in the hospital at the time that her platelet counts were from 70,000 to 90,000 per cubic millimeter. A few megakaryocytes were observed on the film, but in a differential cell count of 500 cells none were found. Both the erythroid and the myeloid elements of the marrow apparently had been stimulated. We do not have any explanation for this finding, but one of us (E. H. F.) has observed the same type of apparent marrow stimulation associated with thrombopenic purpura following ingestion of sedormid (allylisopropylacetylcarbamide).

Analysis of Case 6—Our main reason for including the data on the patient in this case was to call attention to the fact that after administration of the arsenicals hemorrhagic phenomena may occur which are quite distinct from thrombopenic purpura and are due to a different mechanism from that of thrombopenic purpura. For example, this patient exhibited a toxic reaction to neoarsphenamine, bismarsen and mapharsen, but when the dose of neoarsphenamine was cut down to 0.1 Gm (given intravenously) she showed no constitutional reaction, yet hemorrhages into the tissues, evidenced by large ecchymotic areas, took place. When we first examined the patient, her platelet count was below normal, however after administration of 0.1 Gm of neoarsphenamine, the count was not depressed further but rose and did not

return to the original level for twenty-four hours (table 7) No petechial lesions were noted during the experiment The results of the Dalldorf capillary fragility test showed decreased capillary fragility, indicating that were one to consider increased capillary permeability and fragility responsible for the areas of ecchymosis, the toxic action of the arsphenamines on her capillaries must have been local instead of general, for the capillaries other than those in the area of hemorrhage appeared to be normally resistant This type of hemorrhagic reaction to the arsphenamines obviously requires further study

SUMMARY

Data are presented on 5 patients who had purpura haemorrhagica following treatment with arsphenamine derivatives In 2 the condition followed administration of neoarsphenamine, in 3 it occurred after bismarsen was given A sixth case is described in which hemorrhagic phenomena occurred after therapy with bismarsen and neoarsphenamine, without marked decrease of platelets and without purpuric lesions

Each of the 5 patients who exhibited purpura haemorrhagica after administration of the arsphenamines was tested for sensitivity to mapharsen In no instance was there any constitutional reaction, nor were any untoward symptoms observed In none of these 5 patients did the intravenous injection of mapharsen cause marked depression of the platelet count, petechiae of the skin or other evidences of capillary hemorrhage

Our observations and studies in cases 1 to 5, made after test doses of the arsphenamines to which these patients were sensitive, showed that varying degrees of shock occurred, suggesting that the reaction was an allergic phenomenon rather than due to the toxic effects of oxidation or to a changed chemical form of the drug injected The prompt loss of circulatory tone accompanying the reaction appears to be a vasomotor effect, with loss of capillary tonus, dilatation of the capillary bed and a rapid loss of platelets from the general circulation It is difficult to believe that such enormous numbers of platelets could be destroyed within fifteen minutes after the drug is injected The fact that a great number of platelets can be returned promptly into the general circulation by injection of 1 cc of epinephrine hydrochloride (1:1,000 solution), and the rapid rise of the platelet count within twenty-four to forty-eight hours after the reaction are evidence against the assumption of widespread destruction of the platelets

The blood cells other than the platelets showed little if any change during these experiments There appeared to be a tendency to an increase of the polymorphonuclear cells following a reaction, particularly a severe reaction This may well be a phenomenon similar to the leukocytosis associated with protein shock

DEGENERATIVE LESIONS IN THE CERVICAL PORTION OF THE SPINE

THOMAS HORWITZ, M D

PHILADELPHIA

The current concept that the hypertrophic variety of spondylitis (spondylitis osteoarthritis) is not an arthritis but a spondylosis arising as a reaction to changes primarily in the intervertebral disks is based on the views promulgated by Schmorl and his followers¹ The intervertebral disks, through the effect of age and of continuous functional stress, pass through stages of fibrillation, dehydration, fissuring and "brown degeneration" Defects in the cartilage plates, which may be congenital, traumatic or infectious in origin, permit extrusion of disk material into the vertebral bodies and penetration of vessels from the spongiosa into the normally avascular intervertebral disks, which may become calcified or ossified The thinning of the disks and the loss of their normal buffer effect are attended by sclerosis of the adjacent vertebral borders and by marginal proliferation which may proceed to bony ankylosis This progressive series of events has been duplicated experimentally²

The lower part of the cervical and the lumbar region of the spine demonstrate these degenerative changes most frequently, probably because of the greater susceptibility of these regions to functional trauma The attention of most pathologists, clinicians and roentgenologists who have written on this subject has been focused on the lumbar region, especially in its relation to pain low in the back and to the sciatic syndrome Degeneration of the posterior part of the intervertebral disk and increased lordosis of the lumbar portion of the spine have been stressed as factors in the narrowing of the intervertebral foramina associated with direct impingement on the spinal nerves, while the contact of the facet margins against the pedicle above, or the lamina below, after "subluxation" at the zygapophysial joint, has been suggested as

From the Daniel Baugh Institute of Anatomy, Jefferson Medical College

1 (a) Schmorl, G, and Junghanns, H Die gesunde und kranke Wirbelsäule im Roentgenbild, Leipzig, George Thieme, 1932 (b) Junghanns, H Die Pathologie der Wirbelsäule, in Henke, F, and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1939, vol 9, pp 216-429

2 Keyes, D C, and Compere, E L The Normal and Pathological Physiology of the Nucleus Pulposus of the Intervertebral Disc An Anatomical, Clinical and Experimental Study, J Bone & Joint Surg **14** 897, 1932

another factor in the causation of pain in the back. The extensive literature on these various lesions in the lumbar region has been recently reviewed by Saunders and Inman,³ and by me⁴ after an anatomic and roentgenologic study of the lumbar portion of 100 adult human spines.

It is my purpose in this communication to analyze the degenerative changes in the cervical portion of the spines of 50 adult human cadavers. Features of "discogenetic disease" which occur in the cervical region are less well described than those occurring elsewhere in the spine. A few authors,⁵ in recording clinical and roentgenologic observations, have stressed the association of segmental neuritis (as evidenced by pain in the shoulder, arm and precordial regions and by weakness and muscular atrophy) with thinning of the intervertebral spaces, subluxation of the articular facets, narrowing of the intervertebral foramina and formation of exostoses on the anterior and lateral borders of the vertebral bodies of the cervical part of the spine.

PATHOLOGIC AND ANATOMIC ANALYSIS OF THE CERVICAL PORTION OF THE SPINES OF FIFTY ADULT HUMAN CADAVERS

The entire cervical and the upper part of the thoracic region of the spine were removed from 50 male cadavers whose ages varied from 45 to 80 years, with an average of 56 years. These were studied grossly after the removal of all paravertebral soft tissues and then were sectioned in the midsagittal plane.

Changes in the intervertebral disk were noted in 38, or 76 per cent, of the specimens and most frequently involved the lower cervical segments (between the third and the fourth cervical in 8, the fourth and the fifth cervical in 28, the fifth and the sixth cervical in 38, the sixth and the seventh cervical in 18 and between the seventh cervical and the first thoracic in 6). These changes consisted of varying stages of fibrillation, fissuring, brown degeneration, narrowing and ossification, and were associated with proportionate stages both of sclerosis of the adjacent vertebral spongiosa and of marginal bony proliferation. Such

3 Saunders, J., and Inman, V. T. The Intervertebral Disc. Collective Review, Surg., Gynec. & Obst. **69** 14, 1939.

4 (a) Horwitz, T., and Smith, R. M. An Anatomical, Pathological and Roentgenological Study of the Intervertebral Joints of the Lumbar Spine and of the Sacroiliac Joints, Am J Roentgenol **43** 173-186 (Feb.) 1940. (b) Horwitz, T. Lesions of the Intervertebral Disk and Ligamentum Flavum of the Lumbar Vertebrae. Anatomic Study of Seventy-Five Human Cadavers, Surgery **6** 410, 1939.

5 (a) Turner, E. L., and Oppenheimer, A. A Common Lesion of the Cervical Spine Responsible for Segmental Neuritis, Ann Int Med **10** 427, 1936. (b) Oppenheimer, A., and Turner, E. L. Discogenetic Disease of the Cervical Spine with Segmental Neuritis, Am J Roentgenol **37** 484, 1937.

exostosis formation, present in 35, or 70 per cent, of the specimens, was most advanced in the anterolateral portion of the vertebral body and involved especially the lower cervical vertebrae (third cervical in 4, fourth cervical in 14, fifth cervical in 28, sixth cervical in 35, seventh cervical in 35 and first thoracic in 10) Protrusion of intervertebral disk material into the spongiosa of the adjacent vertebral bodies was noted only once (between the fifth and the sixth cervical vertebra)

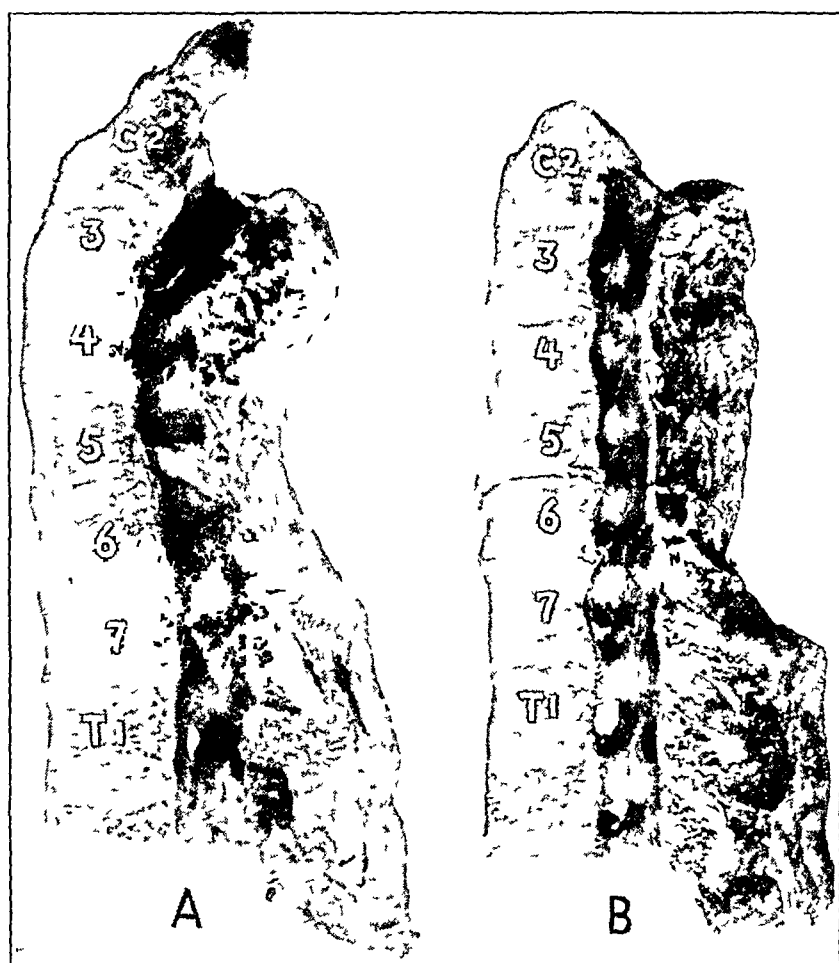


Fig 1—Degenerative changes involving the intervertebral disks *A*, degeneration in the disks between the fifth and the sixth, the sixth and the seventh cervical and the seventh cervical and the first thoracic vertebra, associated with narrowing, fibrillation and "brown degeneration" The disk between the sixth and the seventh cervical vertebra is ossified anteriorly and associated with compression of the seventh cervical body *B*, similar changes in the disks between the fourth and the fifth, the fifth and the sixth and the sixth and the seventh cervical vertebra There is fissuring of the disk between the fifth and the sixth cervical segment, associated with anterior and posterior marginal proliferation

Ossification of the intervertebral disk accompanied by fusion of the adjacent vertebral bodies was observed in three instances (once each between the fifth and the sixth cervical, the sixth and the seventh cer-

vical and the seventh cervical and the first thoracic vertebra) (figs 1 through 5)

Narrowing of the entire intervertebral disk was associated with loss of the normal anterior curvature of the cervical spine and with *widening* of the intervertebral foramens. Loss of the posterior portion of the disk was associated with exaggerated cervical lordosis and with *narrowing* of the intervertebral foramens. Experimentally, the appoxi-

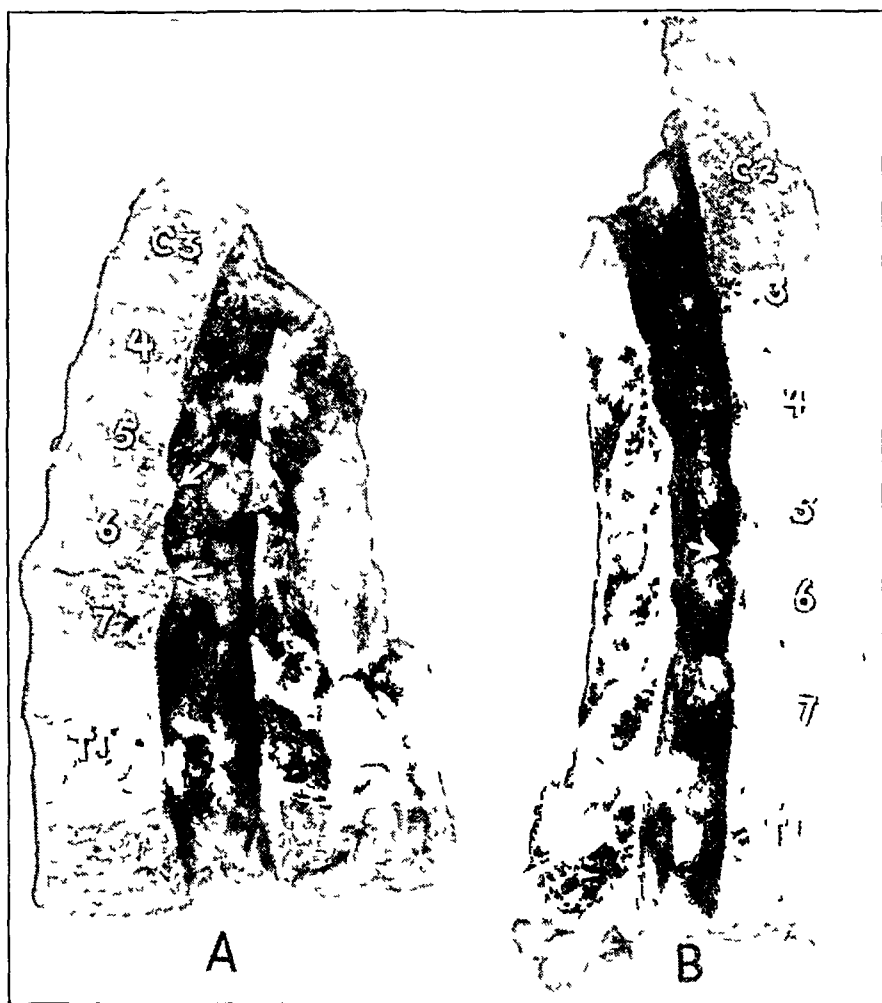


Fig 2—Degenerative changes involving the intervertebral disks of all the cervical vertebrae (A and B). The changes are most marked between the fifth and the sixth and between the sixth and the seventh cervical segment and are associated with anterior and posterior lipping of the upper and the lower margin of the vertebral bodies. The posterior osteophytes and intervertebral disks protrude into the spinal canal and encroach on the lumens of the respective intervertebral foramens.

mation of two normal adjacent vertebrae, after removal of the entire intervening disk, is followed by widening of the intervertebral foramens and not by narrowing. Diminution of the lumen of an intervertebral foramen was more frequently due to encroachment on its anterior surface by posterior lipping of the adjacent vertebral bodies, and to

encroachment on its posterior surface by marginal proliferation of the articular facets covered by ligamentum flavum of normal thickness. Such changes were evident in 20, or 40 per cent, of the specimens (between the third and the fourth cervical vertebra in 4, the fourth and the fifth cervical in 20, the fifth and the sixth cervical in 20, the sixth and the seventh cervical in 16, and the seventh cervical and the first thoracic in 4) (figs 2, 4 and 5). "Posterior displacement" of one vertebra on another was seen once, the posterior margin of the body of

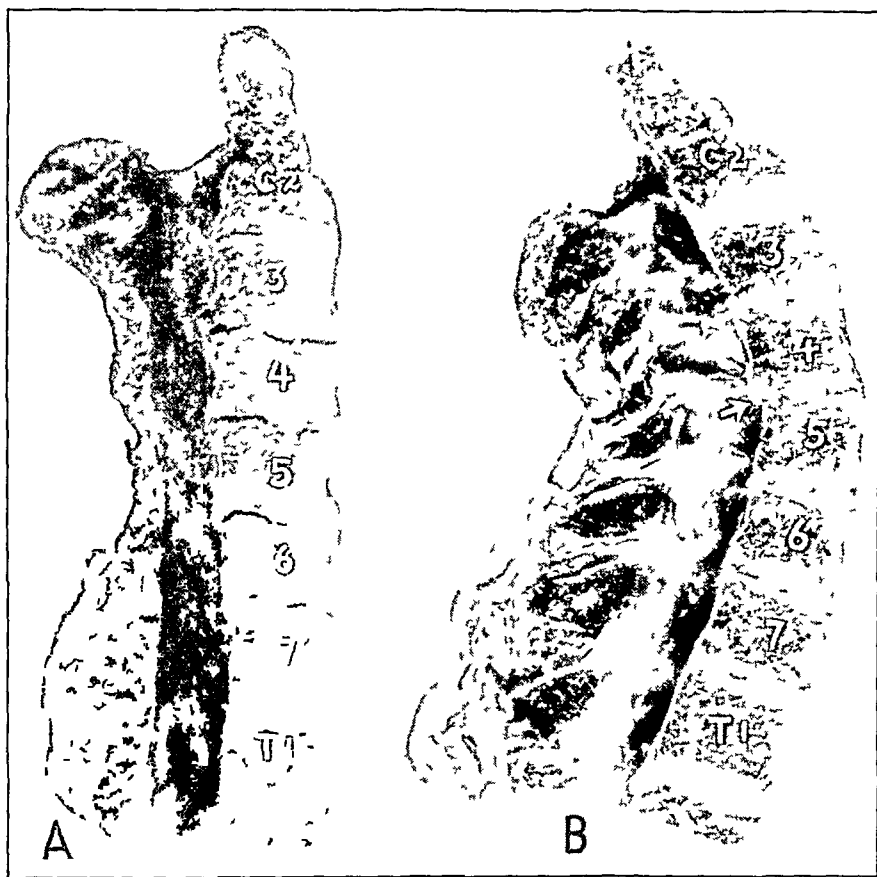


Fig 3—*A*, advanced degeneration of all the intervertebral disks, with approximation of the vertebral bodies and loss of the normal anterior curvature of the cervical spine. *B*, narrowing of the disk between the fourth and the fifth cervical segment, associated with $\frac{1}{8}$ inch (0.32 cm) "posterior displacement" of the body of the fourth cervical on the fifth. No congenital defects are present.

the fourth cervical vertebra lying $\frac{1}{8}$ inch (0.32 cm) posterior to the corresponding margin of the fifth cervical vertebra. There was no associated congenital defect, but there was narrowing and advanced degeneration of the intervening disk (fig 3). No instance of anterior spondylolisthesis was observed. There were no secondary (accessory) epiphyses of the articular or spinous processes of any of the cervical vertebrae.

ROENTGENOGRAPHIC OBSERVATIONS ON THE CERVICAL PORTION OF
THE SPINES OF TWENTY-FIVE ADULT HUMAN CADAVERS

Roentgenograms of the cervical and dorsal portions of the spines of 25 cadavers were made in the anteroposterior, lateral and right and left oblique (45 degrees) planes. Conclusions as to the relative merit of roentgenography in the diagnosis of degenerative lesions in the cervical

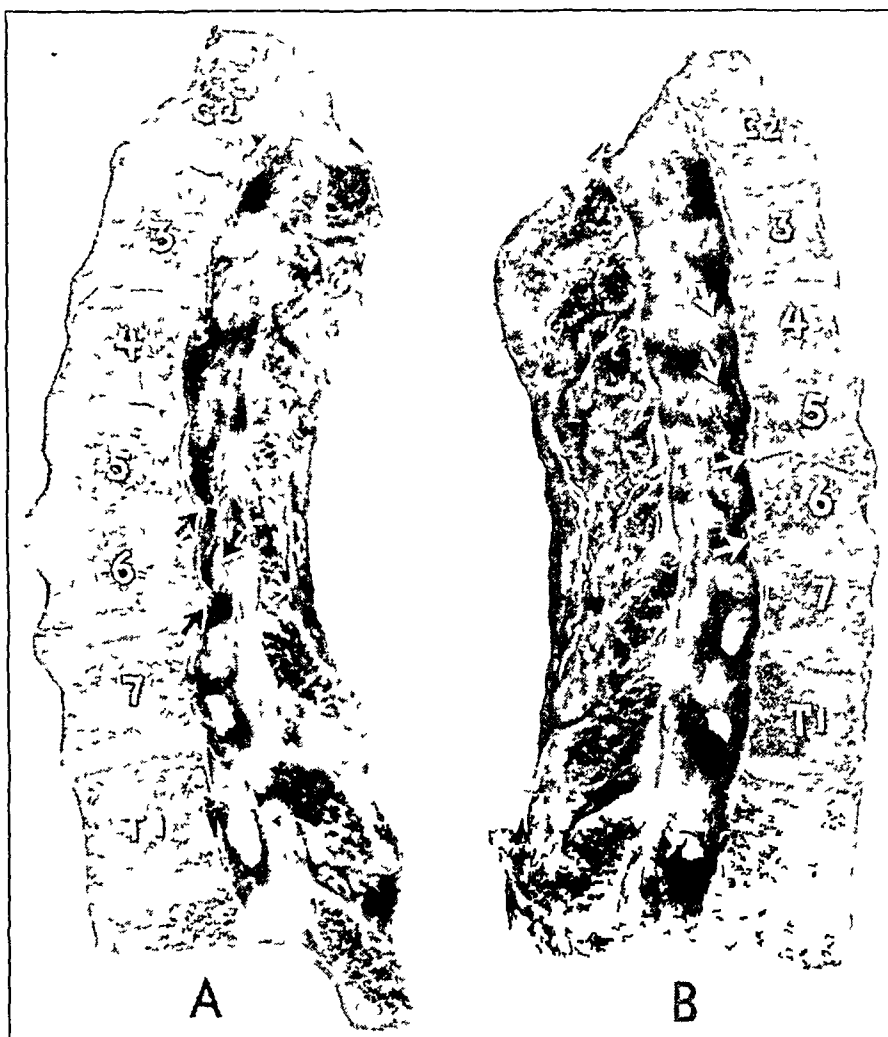


Fig 4—*A* and *B*, degenerative changes (narrowing, fibrillation, fissuring and “brown degeneration”) involving all of the cervical intervertebral disks, and most advanced between the fifth and the sixth and between the sixth and the seventh cervical body, where there is associated anterior and posterior lipping. These posterior bony and disk protrusions are visibly narrowing the lumens of the respective intervertebral foramina. The anterior protrusions of the ligamentum flavum due to underlying marginal proliferation of the articular facets, are well visualized.

part of the spine were identical with those reported after a similar study of the lumbar portion of the spines of 25 human adults.^{4a}

Anatomic and roentgenographic observations were specifically made of the articular processes and zygapophysial joints in the cervical part of

the spine. In a previous communication^{1a} I concluded that the roentgenograms of the lumbar region of the spine taken in the 45 degree oblique plane, as advocated by a number of authors for the visualization of the articular facets and zygapophysial joints, must be evaluated with caution. The frequency in the lumbar vertebrae of curvature of

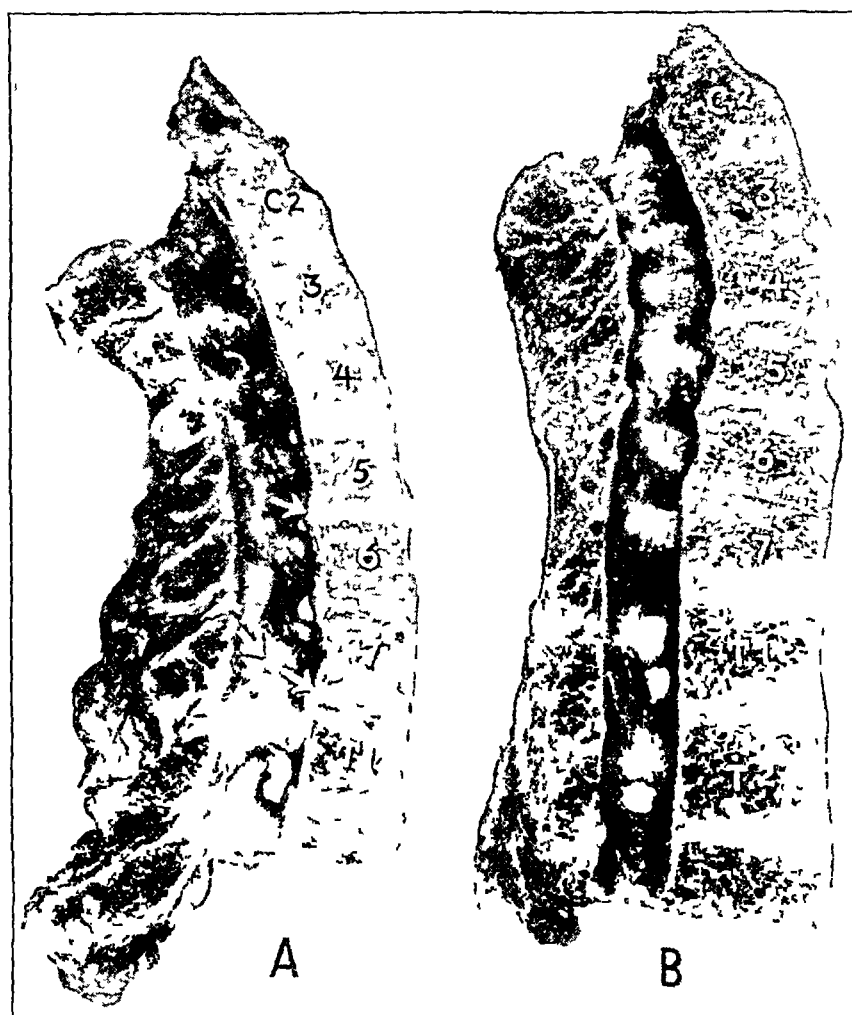


Fig 5—*A*, degenerated intervertebral disks between the fifth and the sixth and between the sixth and the seventh cervical vertebra. These disks and posterior osteophytes at the adjacent vertebral margins bulge posteriorly and encroach on the respective foramina. Anterior bulge of the ligamentum flavum due to marginal proliferation of the underlying articular facets diminishes the lumen of the intervertebral foramen between the seventh cervical and the first thoracic vertebra. The articular facets between the first and the second thoracic vertebra have been denuded to demonstrate the relation of these vertebrae to the foramen. *B*, marked osteoporosis of the vertebrae, associated with advanced degenerative changes in the cervical intervertebral disks. There is compression of the bodies of the sixth and the seventh cervical vertebra. The anterior portion of the disk between the fifth and the sixth cervical segment extends into the adjacent spongiosa above and below, while that between the sixth and the seventh cervical vertebra is ossified anteriorly. The intervertebral disks in the thoracic region, although degenerated, are expanded at the expense of the height of the adjacent osteoporotic vertebral bodies.

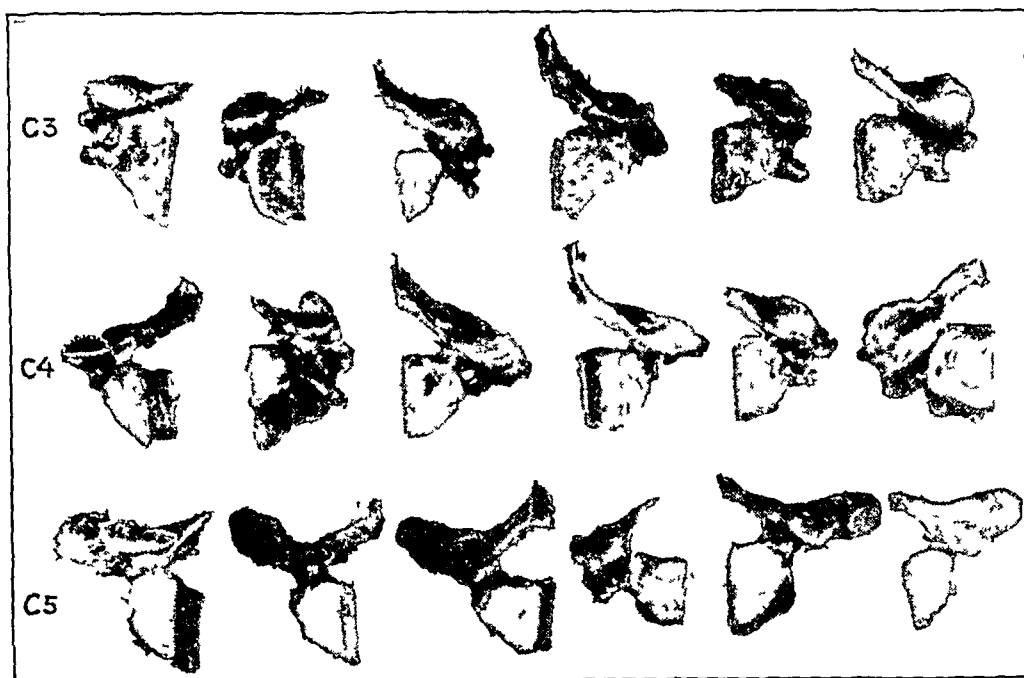


Fig 6—Superior facets of a number of third cervical (top row), fourth cervical (middle row) and fifth cervical (bottom row) vertebrae

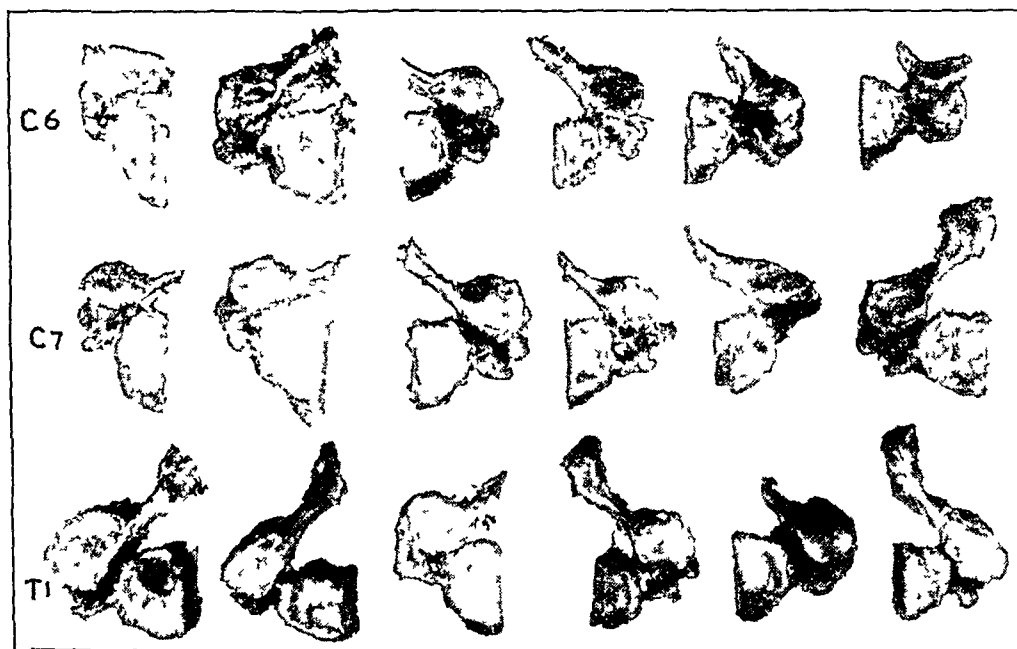


Fig 7—Superior articular facets of a number of sixth cervical (top row), seventh cervical (middle row) and first thoracic (bottom row) vertebrae All the facets in figures 6 and 7 face cephalad (differing to varying degrees in the unmacerated specimens because of the normal anterior curvature of the cervical spine) The superior facets of all the cervical vertebrae are facing dorsalward In the first thoracic segments, the first and second specimens from the left and the last one on the right face outward and dorsalward (thoracic type) Degenerative changes in the articular cartilage and marginal bony proliferation of the facets are most marked in the lower cervical and the first thoracic vertebrae

the articular facet surface and of variation of the zygapophysial joint angle from the normal size of 45 degrees from the sagittal plane, makes impossible the penetration of the roentgen rays in a plane parallel to the joint space. Thus a summation of shadows is created on the roentgenogram which may falsely be interpreted as indicative of pathologic alteration when no such change is present.

These anatomic variations do not occur in the cervical region. The facet surfaces are always flat, and while the articular surfaces face at a variable degree cephalad (superior facet) and caudad (inferior facet), they invariably are directed dorsalward (superior facet) and ventralward (inferior facet) (figs 6 and 7). In the making of a roentgenogram of a direct lateral view of the cervical portion of the spine, the roentgen rays therefore penetrate parallel to the articular surfaces. Narrowing, clouding and obliteration of the joint space, irregularity of the articular margins, sclerosis of the adjacent bones and marginal proliferation of the facets are indicative of pathologic changes. Such roentgenographic findings were most frequently noted in the lower part of the cervical region of the spine and were usually associated with degenerative changes in the intervertebral disks and vertebrae.

Since the facets between the atlas and the epistropheus converge so that the inferior facets of the first cervical vertebrae face downward and medialward, they are best visualized on the anteroposterior view through the open mouth. The facets between the seventh cervical and the first thoracic vertebra are in a transitional zone and may be of either the cervical type or the thoracic type (articular surfaces 20 degrees anterior to the coronal plane), and therefore the roentgenograms must be made in both planes (fig 7). Roentgenograms of the 45 degree oblique views of the cervical portion of the spine visualize best the size and shape of the intervertebral foramina.

COMMENT

Differential Diagnosis of Pain in the Neck, Shoulder and Upper Extremity—Oppenheimer and Turner⁵ ascribed certain cases of segmental neuritis in elderly persons to the thinning of one or more intervertebral spaces of the cervical portion of the spine accompanied by consequent unilateral or bilateral narrowing of the corresponding intervertebral foramina and by compression of nerve roots. Discogenetic disease in the cervical part of the spine may therefore be associated with discomfort, muscular weakness and atrophy in the upper extremities, shoulder girdle, neck and precordium. Constriction of the intervertebral foramen may be consequent on inflammatory and degenerative changes in the zygapophysial joints, even with the intervertebral disks uninvolved. This concept parallels the association, suggested by many authors, between degenerative lesions in the lumbar portion of the spine and backache with pain referred to the lower extremities.

The relation of cervical osteoarthritis to root pain and radicular sensory alterations and the importance of differentiating this syndrome from visceral diseases which it may simulate were previously stressed by Gunther and Kerr,⁶ Nathan,⁷ after the experimental production of nonsuppurative arthritis in animals, concluded that pain in spondylitis may be referred from nerve roots which are compressed as they leave their bony outlets either by inflamed ligaments and capsules or by adhesions, in the infectious variety of spondylitis, and by pressure of osteophytes and of thickened soft tissues in the hypertrophic variety. Gunther and Sampson,⁸ Nachlas,⁹ and Hanflig¹⁰ noted that left-sided segmental neuritis due to cervical arthritis may simulate cardiac disease because of pain referred to the precordium, the left shoulder and the left upper extremity. Bailey and Casamajor,¹¹ Parker and Adson¹² and Morton¹³ reported that soft tissue and bony overgrowth in cervical osteoarthritis may encroach on the spinal canal and simulate other extramedullary lesions of the spinal cord.

The symptoms and signs of segmental neuritis in hypertrophic arthritis of the cervical portion of the spine are not unlike those of a number of other pathologic conditions, viz., the cervical rib syndrome, brachialgia associated with a low position of the shoulder girdle, the scalenus anticus syndrome, brachial plexus neuritis, lesions of the shoulder joint (arthritis, bursitis, lesions of the supraspinatus tendon) and fracture of the clavicle or the first rib. Nathanson¹⁴ indicated that

6 Gunther, L., and Kerr, W. J. The Radicular Syndrome in Hypertrophic Osteo-Arthritis of the Spine. An Analysis of Thirty Cases, *Arch Int Med* **43** 212 (Feb.) 1929.

7 Nathan, P. W. The Neurological Condition Associated with Polyarthritis and Spondylitis, *Am J M Sc* **152** 667, 1916.

8 Gunther, L., and Sampson, J. J. The Radicular Syndrome in Hypertrophic Osteoarthritis of the Spine. Root Pain and Its Differentiation from Heart Pain, *J A M A* **93** 514 (Aug 17) 1929.

9 Nachlas, I. W. Pseudo-Angina Pectoris Originating in the Cervical Spine, *J A M A* **103** 323 (Aug 4) 1934.

10 Hanflig, S. S. Pain in the Shoulder Girdle, Arm and Precordium Due to Cervical Arthritis, *J A M A* **106** 523 (Feb 15) 1936.

11 Bailey, P., and Casamajor, L. Osteoarthritis of the Spine as a Cause of Compression of the Spinal Cord and Its Roots, with Report of Five Cases, *J Nerv & Ment Dis* **38** 588, 1911.

12 Parker, H. L., and Adson, A. W. Compression of the Spinal Cord and Its Roots by Hypertrophic Osteoarthritis. Diagnosis and Treatment, *Surg, Gynec & Obst* **41** 1, 1925.

13 Morton, S. A. Localized Hypertrophic Changes in the Cervical Spine with Compression of the Spinal Cord or of Its Roots, *J Bone & Joint Surg* **18** 893, 1936.

14 Nathanson, L. Pulmonary Apical Tumefaction Simulating Bursitis. Necessity for Routine Chest Examination in Patients with Shoulder Pain, *Quart Bull, Sea View Hosp* **4** 326, 1939.

tumors at the apex of the chest,¹⁵ because of identical symptoms, may mask themselves by the incidental presence of lesions in the cervical portion of the spine or in the shoulder region

The scalenus anticus syndrome, described by Ochsner, Gage and DeBakey,¹⁶ who attributed its original concept and successful treatment by scalenotomy to Naffziger,¹⁷ is characterized by the clinical picture of cervical rib in the absence of such a supernumerary rib, and is due to spasm and hypertrophy of the scalenus anticus muscle, which serves to compress the lower trunks of the brachial plexus and the subclavian artery against the first rib. While this condition may be primary, it is often secondary, according to Freiberg¹⁸ and Bishop¹⁹. Cervical arthritis and lesions of the shoulder girdle may aggravate and perpetuate their symptoms and signs by initiating spasm of the scalenus anticus, and this cycle may or may not be broken by the successful therapy of the underlying lesion

Peripheral Vascular Phenomena Associated with Spondylitis—Because of the known relief of articular symptoms in chronic infectious arthritis after treatment with general and local measures to induce peripheral vasodilatation, Rowntree and Adson²⁰ recommended sympathetic ganglionectomy for those types associated with abnormal alterations of peripheral vascular tonus. Craig and Kernohan²¹ failed to observe any significant histologic changes in the sympathetic ganglions removed in 46 such cases, these authors suggested that the ganglions act merely as relay stations for impulses from higher centers

15 Ray, B. S. Tumors at the Apex of the Chest, *Surg, Gynec & Obst* **67** 577, 1938

16 Ochsner, A., Gage, M., and DeBakey, M. Scalenus Anticus (Naffziger) Syndrome, *Am J Surg* **28** 669, 1935

17 Naffziger, H. C. Neuritis of the Brachial Plexus Mechanical in Origin, *Surg, Gynec & Obst* **67** 722, 1938

18 Freiberg, J. A. The Scalenus Anterior Muscle in Relation to Shoulder and Arm Pain, *J Bone & Joint Surg* **20** 860, 1938

19 Bishop, W. A. Calcification of the Supraspinatus Tendon. Cause, Pathologic Picture and Relation to the Scalenus Anticus Syndrome, *Arch Surg* **39** 231 (Aug.) 1939

20 Rowntree, L. G., and Adson, A. W. Bilateral Lumbar Sympathetic Ganglionectomy and Ramisectomy for Polyarthritis of the Lower Extremities, *J A M A* **88** 694 (March 5) 1927, Polyarthritis. Further Studies on the Effects of Sympathetic Ganglionectomy and Ramisectomy, *ibid* **93** 179 (July 20) 1929, Bilateral Lumbar and Thoracic Sympathetic Ganglionectomy and Ramisectomy for Polyarthritis of the Lower and the Upper Extremities, *Tr A Am Physicians* **44** 221, 1929, The Surgical Indications for Sympathetic Ganglionectomy and Trunk Resection in the Treatment of Chronic Arthritis, *Surg, Gynec & Obst* **50** 204, 1930

21 Craig, W. M., and Kernohan, J. W. The Surgical Removal and Histologic Studies of Sympathetic Ganglia in Raynaud's Disease, Thrombo-Angitis Obliterans, Chronic Infectious Arthritis and Scleroderma, *Surg, Gynec & Obst* **56** 767, 1933

Stewart,²² while performing a lumbar sympathectomy to relieve intermittent claudication and paresthesias in the lower extremities of a 61 year old man, observed the trunk involved in a mass of tissue surrounding the hypertrophic process between the fourth and the fifth lumbar vertebra, and he noted improvement, after extirpation of the left lumbar sympathetic trunk, in the peripheral circulation of the ipsilateral lower extremity

Lipshutz and Naide²³ called attention to the writings of Hesse, Zaiceva and Vinogradov,²⁴ who noted the calorimetric changes in the skin of the lower extremity resulting from irritation or pressure on the lumbar portion of the ganglionated sympathetic cord and its communicating rami. Any lesion which presses on or irritates the lumbar portion of the ganglionated cord may effect change in the temperature of the lower extremity on the side on which the lesion occurs. Irritation by moderate pressure may produce peripheral vasoconstriction, but when the ganglions become destroyed and impulses are interrupted, peripheral vasoconstriction is followed by peripheral vasodilatation. Lipshutz and Naide illustrated such peripheral vascular changes resulting from pressure on the lumbar sympathetic cord in 3 cases, one with a carcinoma of the transverse colon involving the posterior portion of the parietal wall, another with a mass of retroperitoneal lymph nodes and a third with an enormously thickened terminal ileum due to chronic inflammatory disease.

I noted that in the lumbar portion of the spines of a number of adult cadavers in which advanced marginal osteophytes involved the anterolateral portion of the vertebral bodies, the lumbar sympathetic ganglionated cord was frequently involved in these soft tissue and bony masses, and that frequently a segment of the sympathetic trunk was markedly stretched over an enlarged osteophyte. May this relation explain, in the light of the clinical observations of Lipshutz and Naide, the peripheral vascular phenomena occasionally noted in the lower extremities of patients with the atrophic and hypertrophic varieties of spondylitis, as well as the relief of peripheral vascular symptoms after sympathectomy in properly selected cases?

22 Stewart, S. F. Relation of the Sympathetic Nervous System to Hypertrophic Arthritis, *J. Bone & Joint Surg.* **13** 848, 1931.

23 Lipshutz, B., and Naide, M. Clinical Significance of Calorimetric Changes in the Lower Extremity, *Arch. Surg.* **38** 412 (March) 1939.

24 Hesse, E. Ein neues calorimetrisches, durch Druck auf den Sympathicus hervorgerufenen Symptom retroperitonealer raumbeschränkender Erkrankungen, *Klin. Wchnschr.* **8** 1360, 1929. Zaiceva, A. Ueber das Hesse'sche Symptom bei Retroperitonealtumoren, *Zentralbl. f. Chir.* **59** 2685, 1932. Vinogradov, I. P. Das calorimetrische Symptom Hesses bei Geschwulsten und anderen raumbeschränkenden Erkrankungen im Retroperitonealraum, *Deutsche Ztschr. f. Chir.* **246** 634, 1936, cited by Lipshutz and Naide.²³

I also observed the proximity of the stellate and the second thoracic sympathetic ganglions to the costovertebral articulations of the first and the second rib respectively, the ganglions overlying the anterior surfaces of the joints in intimate contact with the joint capsule. May this anatomic relationship explain the peripheral vascular phenomena in the upper extremities occasionally encountered in patients with infectious spondylitis involving the cervicothoracic portion of the spine, and in some patients with hypertrophic arthritis affecting the same region? Proliferative and degenerative changes in the costovertebral joints were associated with comparable lesions in the cervical and thoracic portions of the spine in a number of my specimens, and although such changes were conspicuous in the joint between the rib and the vertebral body (costocentral articulation), they were infrequently found in the articulation between the tubercle of the rib and the transverse process (costotransverse articulation). In some of the specimens the stellate and the second thoracic ganglions were visibly impinged on by extensive marginal bony proliferation and thickening of soft tissue involving the related costovertebral articulations.

Since lesions in the cervical part of the spine may at times initiate spasm of the scalenus anticus muscle,¹⁸ the associated vascular phenomena in the upper extremities in these cases may be due in part or entirely to stimulation of the sympathetic nerves which enter the arm via the lowest trunk of the brachial plexus (Todd²⁵). The observation by Telford and Stopford²⁶ of a separate ramus of unmyelinated sympathetic fibers in the inferior part of the lowest plexus trunk overlying the first rib has not been confirmed by Dr. Andrew J. Ramsay and me after a similar study of the lower part of the trunk of 12 brachial plexuses. The unmyelinated sympathetic fibers were diffused uniformly throughout the nerve trunk. The anomaly in the lower extremity comparable to the scalenus anticus syndrome is spasm of the piriformis muscle associated with the sciatic syndrome. That such spasm of the piriformis muscle may be incidental to the lesions of the lumbar spine, the lumbosacral area and the sacroiliac joints has been suggested by Freiberg.²⁷

SUMMARY

The occurrence of degenerative lesions of the intervertebral disks and vertebrae in the cervical portion of the spine follows a progressive sequence of events. These changes are identical with those occurring

25 Todd, T. W. The Arterial Lesion in Cases of Cervical Rib, *J. Anat. & Physiol.* **47** 250, 1912-1913.

26 Telford, E. D., and Stopford, J. S. B. The Vascular Complications of Cervical Rib, *Brit. J. Surg.* **18** 557, 1931.

27 Freiberg, A. H. Sciatic Pain and Its Relief by Operations on Muscle and Fascia, *Arch. Surg.* **34** 337 (Feb.) 1937.

in the thoracic and the lumbar portion of the vertebral column and are found most frequently in the lower segments of the cervical part of the spine. The concept of segmental neuritis, consequent on mechanical or inflammatory irritation of the nerve roots, as a cause of symptoms and signs referable to the neck, shoulder and upper extremity, parallels the relation which has been suggested between similar degenerative lesions of the lumbar portion of the spine and the "low back" syndrome referable to the lower extremities.

The roentgenograms of the cervical portion of the spine made in the lateral and the 45 degree oblique plane may be relied on to visualize accurately pathologic changes involving the articular processes, zygapophysial joints and intervertebral foramens, because few anatomic variations occur in this region.

The diagnosis of segmental neuritis incidental to "discogenetic disease" of the cervical part of the spine requires a cautious exclusion of a number of other pathologic conditions in the neck, shoulder region and apex of the chest. The interrelation of several of these conditions in the same person may enhance the difficulty of differential diagnosis.

Peripheral vascular phenomena are not infrequently evident in patients with the hypertrophic variety of spondylitis. The suggestion, based on certain observations on the human cadaver, is made that these alterations in vascular tonus may be due to direct mechanical or inflammatory irritation of the sympathetic ganglionated cord. Peripheral vasomotor changes in those cases in which there is complicating spasm of the scalenus anticus or of the piriformis muscle may be due in part or entirely to direct irritation of the sympathetic nerves within the nerve trunks which are compressed.

GLOMERULAR NEPHRITIS FOLLOWING INFECTIONS OF THE SKIN

PALMER HOWARD FUTCHER, M D
NEW YORK

While it is generally accepted that acute infection caused by streptococci precedes acute glomerular nephritis in the majority of cases, the exact course of events linking the infection with the renal disturbance is far from clear. Nor is it known whether once the nephritis has manifested itself, chronic infection remains an important agent in prolonging the disease. Authorities differ in the relative emphasis they place on the role of infection in this respect. Among protagonists of the etiologic importance of foci of infection is Kollert,¹ who distinguished two types of infection. One is the "primary focus," a chronic, often long-standing obscure process, situated perhaps in a paranasal sinus, which renders the subject peculiarly reactive to the machinations of subsequent acute invasion by the same organism. In the latter, "precipitating infection," the second of the two types, Kollert saw a trigger mechanism which sets off the initial attack of nephritis, the stage having already been set by the "primary focus." Kollert asserted that, in order to abort the nephritis, it is mandatory not only to remove any residue of the acute precipitating infection, but also to find and exterminate the less obtrusive "primary focus," which is only rarely identical with the precipitating process. He stated the belief that usually the persistence of the urinary abnormalities is evidence that there is still in the body some remnant of infection. Longcope² has also suggested that the progression of nephritis to a subacute or chronic stage may be accompanied by persistence or exacerbations of the infection.

There is no general agreement, however, that the persistence of infection is the explanation for the evolution of chronic nephritis, since the removal of all ascertainable foci may not change an unfavorable

From the Department of Medicine, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore

1 Kollert, V. *Grundlagen der atiologicalen Behandlung der Nierenentzündung*, Leipzig, Franz Deuticke, 1929, cited by Volhard, F. *Zentralbl f inn Med* **51** 301-308 (April) 1930

2 (a) Longcope, W. T. Some Observations on the Course and Outcome of Hemorrhagic Nephritis, *Internat Clin* **1** 1-16 (March) 1938. (b) Longcope, W. T., O'Brien, D. P., McGuire, J., Hansen, O. C., and Denny, E. R. Relationship of Acute Infections to Glomerular Nephritis, *J Clin Investigation* **5** 7-30 (Dec) 1927

course, this has been pointed out by Winkenwerder and his confrères³ at the Johns Hopkins Hospital. In reviewing Kollert's monograph, Volhard,⁴ who himself subscribed to a theory of the relationship of acute nephritis to infection quite similar to that of Kollert, stated his approval of that author's zeal in eradicating foci of infection in the early stages of nephritis, but he was dubious as to the efficacy of such procedures in the chronic stage. Addis,⁵ while also acknowledging an important initial role of the acute infection, has been a proponent of the self-styled "gloomy hypothesis" that "the continuance over years and decades of a slow disintegration of the architecture of the kidney might be a result of the structural disorganization produced in the initial stage of the disease." By analogy he cited the evidence of the long-continued effects on the kidney of experimental acute uranium poisoning. Further, one might point to the chronic nephritis in rats which has been reported as following injections of a nephrotoxic serum.⁶ However, Addis commented that his own hypothesis is at least partially contradicted by the fact that one cannot consistently forecast the evolution of an acute attack of nephritis in human beings to chronicity or to recovery merely on the basis of the intensity of the disease in its initial stage.

Since it is admittedly extremely difficult to be sure of the complete extinction of any infection involving the respiratory tract, it comes to mind that information on the importance of chronic infection in maintaining pathologic activity in the kidneys might be obtained from the study of cases in which glomerular nephritis has followed infections of the skin or of the subcutaneous tissues. The superficial location of the inflammatory process enables the observer to ascertain with some accuracy the moment at which the cutaneous lesion is healed. If the activity of the nephritis is maintained by an infection of the skin, one would expect eventual complete healing of the renal lesion to follow healing of the skin. Further, one would prophesy a uniformly excellent prognosis for complete recovery in this group of cases as compared with

3 Winkenwerder, W. L., McLeod, N., and Baker, M. Infection and Hemorrhagic Nephritis, *Arch. Int. Med.* **56** 297-326 (Aug.) 1935.

4 (a) Volhard, F. Die doppelseitigen hamatogenen Nierenerkrankungen, in von Bergmann, G., and Staehelin, R. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol. 6, pt. 2. (b) Kollert¹.

5 Addis, T. Haemorrhagic Bright's Disease. I. Natural History, *Bull. Johns Hopkins Hosp.* **49** 203-224 (Oct.) 1931, II. Prognosis, Etiology, and Treatment, *ibid.* **49** 271-285 (Nov.) 1931.

6 Smadel, J. E. Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum. I. Preparation and Immunological Studies of Nephrotoxin, *J. Exper. Med.* **64** 921-942 (Dec.) 1936, III. Pathological Studies of the Acute and Chronic Disease, *ibid.* **65** 541-555 (April) 1937. Smadel, J. E., and Farr, L. E. Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum. II. Clinical and Functional Studies, *ibid.* **65** 527-540 (April) 1937.

those in which glomerular nephritis is associated with persistent or recurring infections of the respiratory tract, since it should be easier to eradicate infections of the skin than infections of the nasopharynx. To test this hypothesis, a search of the literature concerning relevant cases has been made and the reports summarized. Also a study has been made of the records of a selected group of patients treated in the Johns Hopkins Hospital whose disease appeared following an infection of the skin. That there is relatively little information on this subject in the American literature lends greater interest to the investigation.

TABLE 1—*Relative Frequency of Infections of the Skin Preceding Glomerular Nephritis, Tabulated from Various Authors*

Observer	Total Cases of Nephritis	Cases Following Cutaneous Infection	Percentage	Type of Cutaneous Infection	Constitution of Whole Group
Bluhm ²⁰	140	2	1.4	Erysipelas 1, Impetigo, 1	Patients of all ages
Kaumheimer ⁷	223	21	9.4	Impetigo	Children
Volhard and Fahr ^{10a}	204	22	11	Erysipelas, 5 miscellaneous, 17	Chiefly adults
Hill ¹²	75	4	5.3	Impetigo	Children
Osman ¹³	235	11	4.7	Skin and scalp wounds	Children and young adults
Southby and Stanton ¹⁴	103	18	17	Chiefly impetigo	Children
Clausen ¹⁵	102	1	1	Erysipelas	Children
Kollert ¹	80		5.15	Not stated	Not stated
Van Slyke and others ¹⁶	50	0	0		Chiefly adults
Guild ¹¹	34	1	2.9	Furunculosis	Children
Addis ⁵			20	Infected wounds	Not stated
Lichtwitz ¹⁷	167	28	17	Miscellaneous	Not stated
Sutton ⁹	18	5	28	Impetigo	Not stated
Richter ¹⁸	100	1	1	Erysipelas	Adolescents and adults
Present series	153*	11	7.2*	Miscellaneous	Children and adults

*Nephritis of type A only

REVIEW OF THE LITERATURE

Relative Importance of Infections of the Skin in the Causation of Nephritis—It should be emphasized at once that of all the infections of the skin complicated by nephritis, impetigo has been the agent most frequently discussed in the papers to which I have had access. Kaumheimer ⁷ thoroughly reviewed the earlier literature on "impetigo-nephritis" and presented a relatively large series of his own cases ^{7a}

⁷ Kaumheimer, L. Ueber akute Nephritis bei Kindern nach impetiginösen Hauterkrankungen, *Monatschr f Kinderh* **10** 139-153, 1912

^{7a} The subject of impetigo-nephritis was recently reviewed by Silvers, S. H. Impetigo Contagiosa Complicated by Acute Nephritis, *New York State J Med* **39** 1093-1095 (June 1) 1939

Phillips⁸ was one of the first to draw attention to the syndrome in this country. More recently Sutton⁹ reported its occurrence in 5 children. Numerous other examples are recorded in the foreign literature on this specific subject and also in the more general papers on glomerular nephritis. The significance of the preeminence of impetigo-nephritis in the group of cases reported in this paper will be pointed out later in the sections on age incidence, bacteriology and prognosis. Monographs on nephritis¹⁰ describe the disease as following cutaneous infections other than impetigo, such as suppurating wounds of the skin, furunculosis and pyogenic infections superimposed on scabies and eczema, doubtless many so-called cases of impetigo are actually instances of pyoderma complicating other conditions, such as eczema.

That infection of the skin appears to play an important part in the production of glomerular nephritis may be seen from table 1. It should be noted that Addis' figures⁵ dealt only with those cases of nephritis (83 per cent of all his cases) in which there was some ascertainable antecedent infection. Guild's series¹¹ represented a group selected because of survival of the acute stage of nephritis. The data of Volhard and Fahr,^{10a} Hill,¹² Osman,¹³ Southby and Stanton,¹⁴ Clausen,¹⁵ Kollert,¹ Van Slyke and others,¹⁶ Guild,¹¹ Addis,⁵ Lichtwitz¹⁷ and Richter¹⁸ are taken from general articles on glomerular nephritis in which there was

8 Phillips, J. Nephritis, a Complication of Impetigo, with Report of Two Cases, *Cleveland M J* **9** 686-691 (Sept) 1910

9 Sutton, L. E., Jr. Nephritis Complicating Impetigo, *South M J* **27** 798-802 (Sept) 1934

10 (a) Volhard, F., and Fahr, T. *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914. (b) Munk, F. *Pathologie und Klinik der Nierenerkrankungen*, Berlin, Urban & Schwarzenberg, 1925, p. 381. (c) Volhard,^{4a} p. 1245

11 Guild, H. G. The Prognosis of Acute Glomerular Nephritis in Childhood, *Bull Johns Hopkins Hosp* **48** 193-211 (April) 1931

12 Hill, L. W. Studies in the Nephritis of Children, *Am J Dis Child* **17**. 270-294 (April) 1919

13 Osman, A. A. The Aetiology and Prognosis of Acute Nephritis in Children and Young Adults, *Guy's Hosp Rep* **75** 306-312 (July) 1925

14 Southby, R., and Stanton, B. L. Acute Nephritis in Children, with Special Reference to Renal Efficiency Tests, *M J Australia* **1** 127-133 (Jan 30) 1926

15 Clausen, S. W. Nephritis in Children, *Atlantic M J* **29** 201-205 (Jan) 1926

16 Van Slyke, D. D., and others. Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, *Medicine* **9** 257-386 (Sept) 1930

17 Lichtwitz, L. *Die Praxis der Nierenkrankheiten*, Berlin, Julius Springer, 1934, p. 251

18 Richter, A. B. Prognosis in Acute Glomerular Nephritis, in *Medical Papers Dedicated to Henry Asbury Christian*, Baltimore, Waverly Press, Inc., 1936, pp. 268-282

no special emphasis placed on infections of the skin Sommer,¹⁹ reporting on impetigo-nephritis in children, stated that nephritis of this origin is as common as that following tonsillitis In explanation of the relatively low incidence reported by Bluhm²⁰ I can remark only that her paper was written at a period when no very clear distinction was made between glomerular nephritis and other forms of Bright's disease One cannot immediately explain why none of Van Slyke's 50 cases and only 1 of Clausen's and 1 of Richter's fell into the group under consideration There is apparently considerable variability in the incidence of this type of nephritis

Age of Patients with Glomerular Nephritis Secondary to Infection of the Skin—Since impetigo is more common in children than in adults, it is not unreasonable that writers on impetigo-nephritis emphasize that the latter syndrome is commonly one of childhood²¹ Husler^{21b} stated the belief that this type of nephritis is seen most frequently in children between the ages of 4 and 7 years Kaumheimer⁷ noted that infants under 1½ years are relatively immune to impetigo-nephritis Adults, however, may be affected, thus 5 of Hering's 7 patients were adults²² Nephritis secondary to a wound or to pyoderma may be seen at any age

Bacteriologic Observations—It appears that impetigo-nephritis may occur in epidemics Husler^{21b} observed glomerular nephritis in 6 of 16 patients with impetigo seen in the spring of 1915, Eichhorst,²³ in a family of 4 children with impetigo, found mild to severe nephritis in 3 No statistics have been encountered detailing the incidence of nephritis as a complication in a large series of cases of impetigo Hering²² and Phillips⁸ each recovered a "streptococcus" from an impetigo pustule in a single case of impetigo-nephritis, Kohn²⁴ isolated diphtheroid organisms in 1 case Reports on the causes of uncomplicated impetigo contagiosa itself are also somewhat inconclusive It has been stated that both staphylococci and streptococci may cause impetigo and that the former are most commonly isolated in the United States, while the latter pre-

19 Sommer Ueber die Häufigkeit und Eigenart der Impetigo-Nephritis im Kindesalter, Veröffentl a d Geb d Heeressanitäts **85** 178-186, 1931, abstracted, Zentralbl f Haut- u Geschlechtskr **39** 79-80, 1932

20 Bluhm, A Zur Aetiologie des Morbus Brightii, Deutsches Arch f klin Med **47** 193-225, 1891

21 (a) Maier, F Nephritis bei Impetigo contagiosa, München med Wchnschr **64** 215 (Feb 13) 1917 (b) Husler, J Zur Frage der Impetigo-Nephritis, Klin Wchnschr **1** 1826-1828 (Sept 9) 1922 (c) Kaumheimer⁷

22 Hering, E Impetigo-Nephritis, Zentralbl f inn Med **43** 633-636 (Sept 30) 1922

23 Eichhorst, H Ueber Impetigo-Nephritis, Deutsches Arch f klin Med **118** 462-475, 1916

24 Kohn, H Impetigo-Nephritis, Berl klin Wchnschr **58** 28-29 (Jan 10) 1921, Zur Impetigo-Nephritis, *ibid* **58** 131 (Feb 7) 1921

dominate in Europe²⁵ Adamson,²⁶ however, stated the belief that impetigo is in all cases caused primarily by streptococci and that staphylococci represent merely secondary invaders

Prodromal Period—Although it is notoriously difficult to delimit exactly the prodromal period, several of those who have written on impetigo-nephritis have made statements as to the interval elapsing between the onset of the cutaneous infection and the first symptom of renal disease, usually edema Kaumheimer⁷ gave the interval as two to six weeks, Hering²² as four weeks and Maier^{21a} as three to four weeks Husler^{21b} stated that the nephritis appears usually at the height of the impetigo and less commonly after the healing of the skin Cases have been reported in which the interval was only three days,²⁷ on the other hand, not uncommonly a case is reported in which the patient had suffered from episodes of impetigo for many years, only to manifest nephritis in the course of an involvement of the skin not apparently different from the previous uncomplicated attacks⁹ For comparison it is interesting to note that Winkenwerder, McLeod and Baker³ found that of 41 cases of glomerular nephritis selected without reference to the type of preceding infection, in 80 per cent the disease developed after a prodromal period of seven to sixteen days

Course of the Nephritis and Prognosis—Glomerular nephritis following impetigo does not differ in its manifestations from glomerular nephritis secondary to scarlet fever, for instance, or to acute pharyngitis, the physical findings and the changes in the urine are identical Kaumheimer⁷ was unable to find any correlation between the severity or the location of the impetigo and the character of the subsequent nephritis Many authors have emphasized the rapidity with which the signs of the nephritis clear after the healing of the infection of the skin, be it impetigo^{21b} or other types of involvement of the skin^{10c} The prognosis is generally considered excellent,²⁸ most patients leaving the hospital after eight to twelve weeks' stay In considering this reputedly bright outlook for impetigo-nephritis it must be recalled, however, that the prognosis for acute nephritis in children is notably better than that for the same disease in adults¹¹ and that the majority of the reported cases of impetigo-nephritis have concerned children, thus possibly the prognosis is governed not by the type of antecedent infection but merely by the age of the group of patients Kaumheimer⁷ reported 2 fatalities in his series of 21 patients, or a mortality of 9.5 per cent, both deaths

25 Tachau, P The Bacteriology of Impetigo Contagiosa, Brit J Dermat **50** 113-118 (March) 1938

26 Adamson, H G On the Bacteriology of Pemphigus Neonatorum, Brit J Dermat **49** 93-99 (March) 1937

27 Eichhorst²³ Sutton⁹

28 Hering²² Husler^{21b}

occurred in the presence of uremia early in the disease Maier^{21a} lost 2 patients in uremia, in a small series of 7 patients with impetigo-nephritis, and he thought, contrary to general opinion, that the prognosis for this type of nephritis should remain very guarded Many of the patients reported by the authors cited as having recovered left the hospital still showing albumin and red cells in their urine and were not adequately followed up In summary, the information at hand is inadequate to indicate definitely whether the outcome of glomerular nephritis following pyogenic infections of the skin differs in any way from that of nephritis secondary to infection at other sites

PROTOCOLS

The cases which I shall now report from the adult medical service of the Johns Hopkins Hospital represent all the recorded examples of acute hemorrhagic nephritis following infections of the skin which have been observed in that service since 1923 They have been selected from a group of 153 cases of acute hemorrhagic nephritis which followed infection of various sorts and came under observation early in the course of the disease The 153 cases comprise those in Longcope's²⁹ group 1 (of nephritis type A, i e, the type of nephritis which follows an acute infection) in contradistinction to those in his group 2 (nephritis of type B, in which the onset is insidious) In only 2 of our 11 patients (M B and C McK) was there any ascertainable acute infection other than an infection of the skin immediately preceding the onset of the nephritis Each patient was carefully examined for foci of infection other than those in the skin, in 7 patients the pharynx came under suspicion and in 3 patients the teeth The urine of all the patients was sterile Serologic tests for syphilis gave negative results for all patients save 3 (J D, C McK and D T)

In these protocols the urinary phenolsulfonphthalein excretion is expressed as percentage excreted in two hours The urea clearance determinations were performed according to the technic of Van Slyke,³⁰ no correction being made for size when the patient was a child The formed elements in the urine are described as seen in an average high power field during the microscopic examination of a centrifuged speci-

29 Longcope, W T (a) Studies of the Variations in the Antistreptolysin Titre of the Blood Serum from Patients with Hemorrhagic Nephritis I Control Observations on Healthy Individuals and Persons Suffering from Diseases Other than Streptococcal Infections, *J Clin Investigation* **15** 269-275 (May) 1936, II Observations on Patients Suffering from Streptococcal Infections, Rheumatic Fever and Acute and Chronic Hemorrhagic Nephritis, *ibid* **15** 277-294 (May) 1936, (b) footnote 2a

30 Peters, J P, and Van Slyke, D D Quantitative Clinical Chemistry, Baltimore, Williams and Wilkins Company, 1932, vol 2

men In addition, Addis counts³¹ were made on the urinary sediment from time to time Quantitative determinations of urinary protein, when made, were performed according to the rather inaccurate technic of Esbach, save in association with an Addis count, when they were done according to the method of Shevky and Stafford³² as modified by Peters and Van Slyke³⁰ The upper limits of normal for the twelve hour Addis count have been considered as 425,000 red blood cells, 1,835,000 white blood cells, 4,270 casts, and 30 mg of protein³³ Longcope has described the technic of the serum antistreptolysin titrations in this group of cases,²⁹ I have considered 100 units the upper limit of normal The blood pressure recorded for each patient on admission was the highest reading observed during the early days of the stay in the hospital The patients were given an alkaline ash diet routinely, the fluid and salt intake was varied according to the degree of cardiac failure, edema and uremia

CASE 1—*Impetigo, moderately severe nephritis, recovery*

M B, a 9 year old white boy, was admitted on March 5, 1935, with the history that for two weeks he had had impetigo on his face and buttocks, for three days, generalized edema, and for two days, fever and sore throat On admission his temperature was 102 F and his blood pressure 130 systolic and 80 diastolic There was healing impetigo on the face and buttocks, and there was a scarlatiniform rash on the trunk There was slight generalized edema The tonsils were large and red The white blood cell count was 17,000 The specific gravity of the urine was 1.022 There was albuminuria (4 plus), with from 20 to 30 red blood cells, 5 white cells and casts of all sorts The nonprotein nitrogen content of the blood was 27 mg per hundred cubic centimeters, and the phenolsulfonphthalein excretion was 88 per cent Material from the cutaneous lesions was not cultured Cultures of material from the throat revealed beta streptococci persistently until a tonsillectomy was done, April 20, 1935, cultures of the tonsillar tissue removed at operation showed a practically pure growth of beta streptococci and minute beta streptococci The patient had a low elevation of temperature during his stay, but otherwise improvement was rapid The scarlatiniform rash disappeared immediately, by March 9 the edema had disappeared and the impetigo had healed The urine cleared rapidly, an Addis count on May 6, 1935, the day of discharge, was normal save for 13,000 casts, the nephritis was regarded as healed The urea clearance on May 3 was 90 per cent of the normal maximum In May 1939, the urine showed no albumin, and the sediment was normal (It is possible that this patient had true scarlet fever and that the nephritis was secondary to the scarlatina rather than to the impetigo^{33a})

31 Addis, T A Clinical Classification of Bright's Disease, J A M A **85** 163-167 (July 18) 1925

32 Shevky, M C, and Stafford, D D A Clinical Method for the Estimation of Protein in Urine and Other Body Fluids, Arch Int Med **32** 222-225 (Aug) 1923

33 Addis, T The Number of Formed Elements in the Urinary Sediment of Normal Individuals, J Clin Investigation **2** 409-415 (June) 1926

33a Patients M B, C B and S P were reexamined in March, February, and March of 1940 respectively The findings were the same as those noted in 1939

CASE 2—*Popliteal abscess, moderately severe nephritis, recovery*

D T, a 10 year old Negro boy, was admitted to the surgical service on April 12, 1936, with cellulitis of the left leg, a condition which had appeared earlier in the day following a superficial scratch. Hot compresses were applied, and on April 17 an abscess in the left popliteal region was incised, no cultures were made. The patient's temperature fell from an initial 104 F (40 C) but never became quite normal, he was sent home on April 22. The urine contained no albumin or formed elements on examination April 12 and 22, the blood pressure was not recorded. On April 28 a headache began, followed by vomiting and puffiness of the face. The patient was admitted to the medical service April 30, with a temperature of 104.4 F and a blood pressure of 128 systolic and 98 diastolic. There was slight puffiness of the face, and the tonsils were enlarged. The operative wound in the left leg had almost healed. The patient was found to have congenital syphilis. The white blood cell count was 8,700. There was albuminuria (3 plus), and the sediment showed 4 to 6 red cells and 5 white cells, with hyaline and granular casts. The nonprotein nitrogen content of the blood was 41 mg per hundred cubic centimeters, the phenolsulfonphthalein excretion was 70 per cent and the urea clearance 35 to 37 per cent of the normal standard. A culture from the healing abscess showed beta streptococci only. Cultures of material from the throat showed beta streptococci persistently before and after tonsillectomy, performed May 21. (Culture of the tonsillar tissue removed at operation revealed beta streptococci and minute beta streptococci.) After admission the patient's temperature fell to normal in twenty-four hours, the facial edema disappeared, and the wound in the leg healed. The blood pressure was normal after May 7. Several carious deciduous teeth were extracted during his stay. On May 19 the urea clearance was 80 per cent of the normal standard. The urine cleared rapidly. On June 5 an Addis count was normal save for 9,000 casts, the patient's nephritis was regarded as healed, and he was discharged. In March and November 1937 the urine on examination showed no albumin or formed elements, despite the fact that at the time of the November examination the patient had an abscess on his foot from which beta streptococci were isolated.

CASE 3—*Impetigo, severe nephritis, recovery*

B D, an 11 year old Negro girl, whose tonsils had been removed at the age of 5 years, gave the history of having had impetigo on her legs at intervals for several years. Two months before admission crusts appeared on her forehead, on June 18, 1937 generalized edema was noted accompanied by slight soreness of the throat and vomiting. On admission to the hospital, June 25, her temperature was normal and her blood pressure 192 systolic and 96 diastolic. There were a few impetiginous lesions on the head and on one shin. There was generalized edema. A few tonsillar tags remained. The heart was moderately enlarged, and the venous pressure was 215 mm of saline solution. On June 28 the patient had several generalized convulsions, and rales appeared at the bases of the lungs. The white blood cell count was 5,000. The specific gravity of the urine was 1.007, and there were approximately 4.5 Gm of albumin per liter. The urinary sediment showed 15 to 20 red cells and 5 to 8 white cells, with hyaline, granular and cellular casts. The nonprotein nitrogen content of the blood was 128 mg per hundred cubic centimeters, the phenolsulfonphthalein excretion was 70 per cent and the urea clearance 35 to 51 per cent of the normal standard. Cultures of material from the cutaneous lesions showed 80 per cent beta streptococci and 20 per cent *Staphylococcus aureus*. No beta streptococci could be cultured from material from the throat on admission, although they were isolated later during her stay.

After the convulsions, digitalis was administered and a lumbar puncture performed, subsequently improvement was rapid. The edema had disappeared by July 5. Because of the streptococcic cutaneous infection the patient was given sulfanilamide, 24 Gm daily, from June 28 to July 3, the impetigo healed slowly and by August 17, the day of discharge, had disappeared. After July 2 the blood pressure was normal. The urea clearance on June 22 was 85 to 88 per cent of the normal maximum. Although the albuminuria cleared rapidly, microscopic hematuria persisted. There was no accentuation during an attack of acute salpingitis in September. An Addis count on the urinary sediment in June 1938 was normal save for 61 mg of protein, and the nephritis was regarded as healed. The patient has not been examined since.

CASE 4—*Pyoderma, severe nephritis, recovery*

L. G., a 13 year old white girl, who had had scarlet fever and a tonsillectomy at the age of 8, without known complications, acquired, six weeks prior to admission, dermatitis venenata, probably due to sumach, practically the whole body was involved, and some of the lesions became infected. Since the fourth week before admission there had been fever, generalized edema, headache, vomiting and hematuria. On admission Sept 8, 1937, the patient's temperature was 100 F (37.8 C), and the blood pressure was 150 systolic and 105 diastolic. She was pale, her face was puffy, and she had depigmented scars of a healed pyoderma on the extremities and retinal edema and hemorrhages. The tonsillar fossae showed a few tags. The hemoglobin content was 50 per cent, and the white blood cell count was 6,600. The specific gravity of the urine, which was grossly bloody, was 1.015, with albumin (3 plus) and casts of all types. The nonprotein nitrogen content of the blood was 62 mg per hundred cubic centimeters, the phenolsulfonphthalein excretion was 32 per cent and the urea clearance 18 to 24 per cent of the normal standard. Cultures of material from the throat revealed beta streptococci inconstantly. The patient was given one transfusion. She improved rapidly. Her facial edema disappeared, and the hemoglobin rose. The blood pressure was normal on September 29. On October 14 the urea clearance was 63 to 67 per cent of the normal standard, and the phenolsulfonphthalein excretion on October 18 was 66 per cent. However, when the patient left, October 20, against advice, her urine still showed albumin (1 plus) and numerous red blood cells. In May 1939 her health was good, and her urine showed only a faint trace of albumin and no red blood cells or casts. Her nephritis was regarded as probably healed.

CASE 5—*Paronychia, moderately severe nephritis, recovery*

D. G., a 15 year old white girl, who had had sore throat frequently, until a tonsillectomy was performed, at the age of 12, was admitted to the hospital on Dec 29, 1933. Two weeks previously an infection had appeared on the distal phalanx of her left thumb, five days before admission there were generalized edema, headache and anorexia, two days before admission the finger was opened surgically. On admission the patient's temperature was 100.8 F, and the blood pressure was 160 systolic and 100 diastolic. There were marked generalized edema, small tonsillar tags, and several carious teeth (subsequently extracted on February 6). There was a granulating paronychia on the left thumb, and the terminal phalanx was red and swollen. The retinas were essentially normal. The hemoglobin content was 68 per cent, and the white blood cell count was 13,000. The specific gravity of the urine was 1.010, it contained albumin (1 plus), 20 to 30 red blood cells and 3 leukocytes, with hyaline, granular and red blood cell casts. The nonprotein nitrogen content of the blood was 30 mg per hundred cubic centimeters,

the phenolsulfonphthalein excretion was 75 per cent and the urea clearance 46 to 49 per cent of the normal maximum. Cultures of material from the throat on December 30, and Jan 1, 1934 showed a very few colonies of beta streptococci, thereafter, the cultures were constantly negative for that organism. Cultures of material from the site of the paronychia showed beta streptococci, minute beta streptococci and *Staphylococcus albus*. The patient improved rapidly. The blood pressure reached normal on January 6 and remained normal. By January 11 the edema had disappeared. By January 18 the urinary elements had entirely cleared. By January 30 the thumb had healed. An Addis count on discharge, February 23, was normal save for 900,000 red blood cells, and the urea clearance was 54 to 62 per cent of the normal maximum. In December 1935, because of recurrences of sore throat, the patient was readmitted, and a tonsillectomy was performed, no beta streptococci appeared in cultures of the tissue removed at operation. The patient's urine, which had shown a trace of albumin inconstantly during the interval, was normal, and the urea clearance was 68 to 78 per cent of the normal maximum. Her nephritis was regarded as healed.

CASE 6—*Pyoderma, severe nephritis, recovery*

C B, a 25 year old white man, was admitted to the hospital on Jan 30, 1933. In 1925 he had had a tonsillectomy, at that time his blood pressure was 110 systolic and 80 diastolic, and his urine was normal as to albumin and sediment. Eight months before admission he and other members of his family suffered an itching eruption of the skin, in his case the eruption soon became covered with crusts. On Dec 27, 1932, he was seen in the dermatology clinic, and his condition was diagnosed as coccogenous dermatitis and abdominal cellulitis, probably complicating scabies. He was treated with sulfur ointment. Seven days before admission the patient noted dyspnea, vomiting, generalized edema, oliguria and hematuria. On admission the temperature was 101.4 F and the blood pressure 205 systolic and 130 diastolic. There were generalized edema, a pyoderma of the extremities with crusts and healing lesions, mild pulmonary edema and retinal edema, with one retinal hemorrhage. The tonsils had been cleanly removed. The white blood cell count was 10,800. The urine was grossly bloody, had a specific gravity of 1.020, and showed approximately 6 Gm of albumin per liter and numerous casts, including red blood cell casts. The nonprotein nitrogen content of the blood was 50 mg per hundred cubic centimeters, the phenolsulfonphthalein excretion was 45 per cent and the urea clearance 40 to 41 per cent of the normal standard. Cultures of the skin revealed an almost pure growth of beta streptococci with a few colonies of *Staphylococcus aureus*. Cultures of material from the throat showed small numbers of beta streptococci persistently. Digitalis U S P was administered, and the cutaneous lesions were treated locally. There was rapid improvement, the temperature soon fell to normal, and by Feb 8, 1933 the edema had disappeared. The blood pressure fell, reaching 130 systolic and 90 diastolic by February 23, it never remained consistently below that level. By March 25 the cutaneous lesions had healed. The urine cleared only slowly and showed red cells on the patient's discharge from the hospital, May 16. The urea clearance had risen to 58 per cent of the normal standard and the phenolsulfonphthalein excretion to 77 per cent. The urea clearance was 97 to 103 per cent of the normal standard in January 1934, and the Addis count was normal save for 45 mg of protein per hundred cubic centimeters. The nephritis was considered healed. In May 1939, when the patient was last seen, his blood pressure as observed at a single examination was 140 systolic and 100 diastolic, and his urine was normal. He was recovering from a drinking bout at the time and appeared agitated by the examination.^{33a}

CASE 7—*Axillary abscess, moderately severe nephritis, recovery*

H M, a 31 year old Negro, had transient lymphangitis of the left arm immediately following cutting of a finger on March 2, 1929. On March 10 he noticed a mass in the left anterior axilla, and on March 12 an axillary abscess was incised and drained in the outpatient department, the pus was not cultured. On March 13 generalized edema developed and subsequently headache, cough and dyspnea. On admission, March 20, the patient's temperature was normal and the blood pressure 150 systolic and 100 diastolic. There was generalized edema. The injured finger was healed and the left axillary abscess nearly so. The tonsils were enlarged but not reddened. There was one retinal hemorrhage. There was a rectal fistula. The white blood cell count was 11,100. The specific gravity of the urine was 1.010. There was albuminuria (2 plus). In the sediment there were 2 to 3 red cells, 6 to 8 white cells, and many casts, including the cellular variety. The nonprotein nitrogen content of the blood was 30 mg per hundred cubic centimeters, and the phenolsulfonphthalein excretion was 50 per cent. Cultures of material from the healing abscess showed beta streptococci (1 plus) and hemolytic *Staph aureus* (2 plus). Cultures of material from the throat occasionally revealed beta streptococci. (In October 1931, after tonsillectomy, culture of the removed tissue showed no beta streptococci.) The patient rapidly improved after admission. By March 31 the abscess had entirely healed, the rectal fistula persisted. By April 1, 1929, the edema had disappeared and after April 2 the blood pressure was normal. The phenolsulfonphthalein excretion on May 27 was 60 per cent. On discharge, June 21, there was still a trace of albumin as well as a few red cells in the urine. These, too, finally disappeared, in October 1931, the Addis count was normal save for 31,900 casts, and the urea clearance was 80 per cent of the normal maximum. His nephritis was regarded as healed. The patient was last seen in February 1936, when the urine showed a faint trace of albumin and no red cells or casts.

CASE 8—*Erysipelas, severe nephritis, recovery*

J D, a 32 year old Negro, was stricken on Dec 26, 1932 with a typical attack of erysipelas involving the face. On admission to another hospital, December 31, his temperature was 102.6 F. He was treated with "erysipelas antitoxin" and made a rapid recovery. A specimen of urine examined on Jan 1, 1933 showed no albumin, while one obtained on January 6 contained a trace, neither specimen showed red cells or casts. He was discharged from the hospital on January 7. On January 12 he noticed edema of his legs, and on January 18 he was admitted to the Johns Hopkins Hospital. At this time his temperature was normal, and the blood pressure 190 systolic and 130 diastolic. The cutaneous lesion had healed, however, there were edema of the legs, moderate dilatation of the heart and hemorrhages and exudates in the eyegrounds. The tonsils were not enlarged. The white blood cell count was 5,800. The urine showed a specific gravity of 1.017, albumin (1 plus), 25 to 35 red cells and 4 white cells, with many hyaline, granular and red cell casts. The nonprotein nitrogen content of the blood was 30 mg per hundred cubic centimeters, the phenolsulfonphthalein excretion was 65 per cent and the urea clearance 38 to 42 per cent of the normal maximum. Beta streptococci could not be isolated from the throat. The Wassermann reaction of the blood was positive, and the patient had a history of inadequately treated syphilis. He made a rapid recovery. The blood pressure reached normal levels on January 26, and by January 29 the edema had disappeared. On March 7 the urea clearance was 90 to 92 per cent of the normal standard. The urine contained no albumin after the second day of the patient's stay in the hospital but continued to show red cells

when he was discharged as asymptomatic on April 5, 1933. In April 1934 he survived bacteremia caused by *Salmonella supestifei*, with no evidence of any renal disease during its course. An Addis count of the urinary sediment in May 1934 was normal save for a slight increase in the protein to 40 mg. His nephritis was considered healed. The patient was last seen in May 1939, when his urine was normal.

CASE 9—*Pyoderma, severe nephritis, recovery*

C McK, a 60 year old Negro, was first seen in the outpatient department in 1935 with the complaint of dyspnea. He was markedly obese, his blood pressure was 120 systolic and 90 diastolic, and his heart was normal. His urine showed no albumin. In 1936 ulcers appeared on the lower part of his right leg and were persistent. Three weeks before admission the area involved by these ulcers became edematous. Two weeks before admission he had a head cold and slight soreness of the throat lasting one day. Six days before admission he noticed turbidity of the urine, headache, increased dyspnea with cough and, finally, edema of the ankles. On admission, Feb 25, 1938, his temperature was 101 F and his blood pressure 210 systolic and 140 diastolic. He was markedly obese and moderately orthopneic, with a nonproductive cough. There was pitting edema over the legs. The tonsils were small. On the right shin there was a 15 cm band of healing and crusted shallow ulcerations. There was arteriovenous compression of the retinal vessels, although the peripheral vessels were not sclerosed. The heart was moderately enlarged. The venous pressure was 215 mm of saline solution. The white blood cell count was 6,100. The urine had a specific gravity of 1.026, it showed approximately 2 Gm of albumin per liter, 90 red blood cells and 15 white blood cells, with hyaline, granular and red blood cell casts. The Wassermann reaction of the blood was positive. The nonprotein nitrogen content of the blood was 32 mg per hundred cubic centimeters, the phenol-sulfonphthalein excretion was 61 per cent and the urea clearance 60 per cent of the normal standard. Beta streptococci were isolated from the lesions on the leg in pure culture, none were observed in cultures of material from the throat. The patient was given digitalis, and sulfanilamide, 3.6 Gm daily, from February 28 to March 8. There was rapid improvement. The blood pressure reached normal on March 8 and remained so. By March 18 the ulcers had healed, and by March 25 the edema had disappeared. On the patient's discharge, April 26, the urea clearance had risen to 85 and 110 per cent of the normal standard, and the urine showed only a few red blood cells and a trace of albumin. In August the ulcers reappeared on his leg, at the same site, only *Bacillus coli* could be isolated from them. There was no flare-up in the nephritis. In May 1939 the ulcers had healed, the urine was normal for the first time, and the nephritis was considered healed.

CASE 10—*Erysipelas, mild nephritis, recovery*

S P, a 45 year old white woman, noted the onset of an attack of erysipelas of the face on Nov 11, 1933. The lesion spread, and the patient began to vomit. On her admission to the hospital, November 15, the disease being of four days' duration, her temperature was 100 F and her blood pressure 120 systolic and 60 diastolic. There was considerable involvement of the face by the erysipelas, and the patient seemed lethargic. There was no edema, save of the face. The tonsils were not enlarged. The white blood cell count was 11,400. The urine was grossly bloody, had a specific gravity of 1.010, and showed albumin (2 plus) and many granular casts. The nonprotein nitrogen content of the blood was 66 mg, the phenolsulfonphthalein excretion was 30 per cent and the urea clearance 21 per

cent of the normal standard. No cultures of skin were made, cultures of material from the throat showed beta streptococci inconstantly. By November 23 the erysipelas had healed, and thereafter the patient was asymptomatic. By December 5 the nonprotein nitrogen content of the blood had fallen to 36 mg per hundred cubic centimeters. Four periapically infected teeth were removed. On her discharge, Jan 24, 1934, the phenolsulfonphthalein excretion was 65 per cent but the urea clearance only 42 to 48 per cent of the normal standard. Although the gross hematuria subsided twenty-four hours after her admission, the patient showed microscopic hematuria during her entire stay. By March 1934 her urine showed no albumin or red blood cells, her nephritis was regarded as healed. In June 1938 her blood pressure, which had always been normal, was discovered to be 175 systolic and 100 diastolic, and there was a faint trace of albumin in the urine, she complained of menopausal symptoms. In May 1939 the menopausal symptoms were still present. Her blood pressure was very labile, varying from 155 systolic and 98 diastolic to 195 systolic and 120 diastolic during a two days' stay in the hospital. The urea clearance was 48 to 64 per cent of the normal maximum, and an Addis count was normal save for 55 mg of protein^{33b}.

CASE 11—*Pyoderma, severe nephritis, becoming quiescent*

T McK, a 33 year old white man with a history of alcoholism, had had furuncles on his buttocks since March 1932. For eight months previous to his admission to the medical service he had had chronic dermatitis on his left forearm, the disease had started as a "boil." Since Christmas 1933 he had had edema of the face and ankles. In January 1934 his blood pressure was 196 systolic and 126 diastolic, and albuminuria and microscopic hematuria were noted. The edema persisted, and he was admitted to the medical service on March 13. His temperature on admission was normal and his blood pressure 152 systolic and 94 diastolic. There was slight edema of the ankles, together with general boggy of the tissues. On the flexor surface of the left forearm there was a circumscribed, elevated and crusted reddish eruption, measuring 5 by 2.5 cm. The tonsils were not enlarged. There was a pilonidal sinus (removed on April 25). The white blood cell count was 8,100. The urine showed a specific gravity of 1.010, and contained approximately 0.2 Gm of albumin per liter. In the sediment there were 30 to 40 red blood cells and 10 white blood cells, with hyaline, granular and red blood cell casts. The nonprotein nitrogen content of the blood was 34 mg per hundred cubic centimeters, the phenolsulfonphthalein excretion was 48 per cent and the urea clearance 60 to 65 per cent of the normal standard. These levels persisted during the patient's stay, as did the urinary elements and the hypertension. Beta streptococci were repeatedly isolated from the lesion on the arm, which did not respond to hot compresses and ultraviolet ray therapy. On May 26 the area of dermatitis was excised and the site successfully grafted with skin. The skin removed at operation revealed numerous abscesses about the hair follicles, and cultures of the specimen showed beta streptococci with a predominance of *Staph aureus*. Beta streptococci were not found in cultures of material from the throat, the furuncles on the buttocks or the pilonidal sinus. On discharge, June 23, the patient's condition was essentially unchanged from that on admission. In April 1935, although he was asymptomatic, his blood pressure was 155 systolic and 100 diastolic, and there was marked albuminuria as well as microscopic hematuria, with the renal functional tests giving the same results as previously. The nephritis was classified as chronic, and the prognosis seemed gloomy. However, when the patient was next seen, in June 1939, he appeared healthy, and there was no infection of the skin. The highest blood pressure obtained during his three days stay in the

hospital was 135 systolic and 90 diastolic. An Addis count showed 1,108 mg of protein, 352,000 red blood cells, 704,000 leukocytes and 110,000 casts, 88 per cent of the latter were of the hyaline variety and the rest granular. The phenolsulfonphthalein excretion was 59 per cent and the urea clearance 78 to 86 per cent of the normal maximum. With the presence of albumin and casts in the urine as the only evidence of renal abnormality, the patient's nephritis was classified as quiescent, in the course of the four years since he was last seen, there had been definite regression of the signs of renal damage.

RECAPITULATION OF THE CASES PRESENTED (TABLE 2)

Incidence of Type of Nephritis—Infected wounds and infections of the skin preceded the onset of symptoms in 11 of the 153 patients with type A glomerular nephritis (group 1), or in 7.2 per cent. Type A nephritis of Longcope²⁹ is that which follows an acute infection. In 4 of the patients (B D, C B, C McK and T McK) the infection of the skin had existed for a relatively long period, varying from two to twenty-four months, before the onset of symptoms of renal disease, the infections can therefore hardly be called "acute." However, since the nephritis which followed them had the sudden onset and other characteristics of type A, rather than those of type B, in which the onset is insidious and the outcome usually very unfavorable, I have classed the 4 patients in question along with the other 7 in group 1. Four of the patients had pyoderma, 2 infections following wounds, 1 a paronychia, 2 impetigo and 2 erysipelas. It should be noted that in the few days preceding their admission to the hospital, 2 patients (M B and C McK) had mild sore throat, the relationship of pharyngeal foci of infection to the nephritis is discussed in the paragraph on the bacteria present.

Age of the Patients—The age of the 11 patients varied from 9 to 60 years, 6 of them were 25 years or older. Since patients under 12 years of age are only rarely admitted to the adult medical service, our series is unduly weighted in favor of the older age groups.

Bacteria Present—For 4 of the patients no cultures of the cutaneous lesions were made. Two of the 4 (J D and S P) had erysipelas, the pyoderma of a third (L G) had completely healed before admission. Of the remaining 7 patients, beta hemolytic streptococci were obtained in pure culture from the skin of 2 and these organisms in association with staphylococci from the skin of 5. Although none of the patients had a severe sore throat before the onset of nephritis, 2 of them (M B and C McK) did have mild pharyngitis in the few days before admission, the tonsils of M B were enlarged and red on admission, and from them beta streptococci were cultured. With the exception of this infection in M B, there was no evidence that acute pharyngitis contributed to the onset of nephritis, but in the cases of 4 of the patients (M B, D T, D G and H M) it was thought advisable, at one point or another in the course

TABLE 2—Summary of Eleven Cases of Glomerular Nephritis Following Cutaneous Infection

Classification	Name	Age	Sex	Race	Type of Cutaneous Infection	Bacteria Found in Cultures of Infected Skin	Other Foci of Infection with Beta Streptococcus	Prodromal Period	Total Duration of Cutaneous Infection	Duration of Cutaneous Infection After Onset of Nephritis	Duration of Symptoms of Active Nephritis†	Total Duration of "Healing"	Highest Antistreptolysin Titer, Units
Severe and moderately severe, with recovery	M B	9	M	W	Impetigo	None	Pharynx	11 days	24 days	13 days	7 days	57 days	500
	D T	10	M	N	Abscess following wound	Beta streptococcus	Pharynx	16 days	32 days	16 days	9 days	38 days	250
	B D	11	F	N	Impetigo	Beta streptococcus, Staph aureus	Pharynx	Less than 60 days	Less than 1 months (?)	Less than 60 days (?)	17 days	12 months	200
	L G	13	F	N	Pyoderma	None	Pharynx	14 days	42 days	23 days	49 days	20 months	
	D G	15	F	W	Paronychia	Beta streptococcus, minute beta streptococcus, Staph aureus	Pharynx, tran siently	9 days	46 days	37 days	18 days	24 months	25
	C B	25	M	W	Pyoderma	Beta streptococcus, Staph aureus	Pharynx	Less than 8 months	10 months	60 days	31 days	12 months	100
	H M	31	M	N	Abscess following wound	Beta streptococcus, Staph aureus	Pharynx	11 days	29 days	18 days	20 days	29 months	
	J D	32	M	N	Erysipelas	None	None	17 days	12 days	Healed before onset	17 days	15 months	500
	O McK	60	M	N	Pyoderma	Beta streptococcus	None	Less than 24 months	25 months	27 days	34 days	17 months	250
Mild with recovery	S P	45	F	W	Erysipelas	None	Pharynx	? 1 days*	12 days	? 8 days*	21 days†	1 months	25
Severe, becoming quiescent	T McK	38	M	W	Pyoderma	Beta streptococcus, Staph aureus	None	Less than 6 months	11 months	5 months	More than 16 months	Quiescent	250

* Nephritis was present on admission

† Edema, hypertension and azotemia were noted

‡ The nonprotein nitrogen content of the blood was normal by Dec 6, 1933

of the disease, to perform tonsillectomy. In addition, the fact that beta hemolytic streptococci were repeatedly isolated from the throats of 7 of the 11 patients justly throws some doubt on the statement that the skin was the only significant focus of infection in these subjects. It has been stated by Long and Bliss³⁴ that in the winter months 10 to 13 per cent of cultures of material taken from the throats of normal persons in Baltimore show beta hemolytic streptococci. Winkenwerder, McLeod and Baker,³ in a study of 22 patients who had recovered from glomerular nephritis, including 1 patient from this series of 11 patients, found that 7, or 32 per cent, of the patients had throat cultures positive for beta streptococci after recovery.

Prodromal Period—In 6 of the patients the prodromal period varied from nine to seventeen days, an additional patient was admitted on the fourth day of erysipelas with signs of nephritis already present. In the remaining 4 patients, relatively chronic dermatitis had been extant for from two months to two years. With regard to the last group, there is, of course, no means of ascertaining whether beta hemolytic streptococci were present in the cutaneous lesions during the whole period of their duration. It is interesting that the patient B D had had several attacks of impetigo prior to that complicated by nephritis.

Course of the Nephritis—None of these infections of the skin seemed to distinguish itself in severity or in any other way from infections of the same category not followed by nephritis. There was no constant story of previous susceptibility to streptococcic infections of other types, such as sore throat. The nephritis itself was typical acute glomerular nephritis of varying severity, with the usual urinary findings in all the patients, hypertension in 9 and evidence of cardiac insufficiency in 3. There was edema in 9 patients, and 3 had marked temporary depression of renal function with nitrogen retention. The disease was classified as severe in 6 patients, moderately severe in 4 and mild in 1.

The disease of 1 patient, T McK, remained in a quiescent stage. The remaining 10 patients, representing 91 per cent of our very small series, recovered. (Longcope^{2a} in 1938 estimated that complete recovery occurred in 55 to 65 per cent of all the patients with nephritis of type A.) Within seven weeks after the onset of symptoms of nephritis, 10 of the 11 patients had become asymptomatic and were well except for the persistence of mild albuminuria and hematuria, in 7 of the patients the signs of renal disease, other than the urinary ones, were of less than three weeks' duration. The total duration of the nephritis from the time of

34 Long, P. H., and Bliss, E. A. Studies upon Minute Hemolytic Streptococci. IV. Further Observations upon the Distribution of Ordinary and Minute Beta Hemolytic Streptococci in Normal and Diseased Human Beings, *J. Infect. Dis.* 62: 52-57 (Jan-Feb) 1938.

onset to the time at which the process was classified as completely healed was less than six months in 3 patients, twelve months in 2, twenty-four months in 4 and twenty-nine months in 1. Three patients (J D, H M and S P) showed a faint trace of urinary albumin irregularly on dispensary visits following the date on which they had been classified as "recovered." Two additional patients (B D and L G), had a very faint trace of albumin in the urine when last seen, but since their disease was of relatively recent origin and improvement had been progressive, they have been classified as "recovered" for the purposes of this paper. In 2 patients classified as "recovered," an elevation in the previously normal blood pressure was noted on examination five years after the acute stage of the nephritis. One of these patients (S P) was passing through the menopause, the blood pressure of the other patient (C B) was determined only once, at a time when he was obviously mentally perturbed.

COMMENT

Earlier in the paper I stated that it was hoped that a study of these cases of nephritis following infections of the skin might throw light on the relationship of a persistent focus of infection to the evolution of chronic nephritis. Two factors tend to vitiate any pertinent conclusions which might be drawn—first, the brevity of the series and, second, the fact that beta hemolytic streptococci were persistently isolated from another focus than the skin, the pharynx, in 7 of the 11 patients. I can point to only one observation as possibly bearing on the role of persistence of infection in promoting pathologic activity. The only patient who has not recovered (T McK, whose nephritis is now in the quiescent stage) represents the 1 patient of the 11 patients whose cutaneous infection persisted for longer than two months after the onset of nephritis, his infection was present for five months after he first noted edema (table 2). Although the only demonstrable focus of hemolytic streptococci, an area of localized dermatitis on his arm, was finally excised surgically and the denuded area successfully grafted with skin, his nephritis has never completely healed. The fact that his urine still contains albumin and casts five years after removal of the focus of streptococcic infection suggests that irreparable damage to the kidneys had been done previous to excision of the infected skin.

Before concluding, it should be noted that a study of table 2 bears out the well known fact that the process of healing of the renal lesions of glomerular nephritis entails a period of several months. Slight albuminuria or microscopic hematuria outlasted the lesion of the skin by one to two years in 7 of the 10 patients whose nephritis finally healed.

SUMMARY

The literature on the occurrence of glomerular nephritis following infections of the skin has been reviewed

The protocols of 11 patients in whom acute and often severe hemorrhagic nephritis followed infected wounds and infections of the skin have been presented, with comments

Beta hemolytic streptococci were isolated from the cutaneous lesions of 7 of the 11 patients, twice in pure culture and five times in association with staphylococci. Two of the 4 patients for whom no cultures of the skin were made had erysipelas

The nephritis is believed to have healed in 10 of the 11 patients and to have become quiescent in 1 patient. The single patient whose urine still shows significant abnormalities is the only one in whom the infection of the skin did not heal within two months after the onset of symptoms of nephritis

BLOOD

REVIEW OF RECENT LITERATURE

RAPHAEL ISAACS, M D

CYRUS C STURGIS, M D

FRANK H BETHELL, M D

AND

S MILTON GOLDHAMER, M D

ANN ARBOR, MICH

The trend in hematology in 1939 was toward the experimental and chemical aspects of the physiology and pathology of the blood and of the blood-forming organs. Studies of material obtained by aspiration of sternal marrow have become an integral part of the analysis of disease. The present review contains data from selected articles published in 1939, with a few from previous years. With the growth of the literature on blood, the number of articles published has increased to such an extent that it has been necessary to omit some publications which no doubt contain material of interest and value. Some of these will be abstracted in later reviews.

PERNICIOUS ANEMIA

A most scholarly consideration of the more important facts and theories concerning knowledge of the etiologic factors in pernicious anemia is given by Meulengracht¹. His presentation deserves a thoughtful perusal by all physicians who are interested in following the remarkable recent development of new information dealing with the etiology of the disease. It is his belief that sufficient data are available to picture the normal process which controls the development of the erythrocytes as follows: (1) the extrinsic factor is supplied by the food, (2) the intrinsic factor is produced by the pyloric glands, that is, glands located in the pylorus, in the duodenum and to a lesser extent in the cardiac

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan

1 Meulengracht, E. Histologic Investigations into Pyloric Gland Organ in Pernicious Anemia, *Nord med (Hospitalstid)* **1** 11, 1939, Histologic Investigation into Pyloric Gland Organ (and Brunner's Glands), *Am J M Sc* **197** 201, 1939, Etiological Factors in Pernicious Anemia, in a Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p 72

region of the stomach, (3) an interaction between these two factors occurs in the small intestine, whereby the ultimate principle is elaborated, (4) this principle is then absorbed from the small intestine, especially from the ileum, (5) this principle is then carried by the blood to the liver and other organs, where (6) it is stored for further use

On the basis of the familial incidence of pernicious anemia, the prevalence of achlorhydria in blood relatives and the fact that the achylia precedes the development of pernicious anemia by ten years, twenty years or longer, he expresses the belief that there is a hereditary defect in the stomach which is transmitted from one generation to another. A review of his own fundamental work is given, which indicates that the intrinsic factor is the product of the pyloric glands in the stomach and of Brunner's glands in the duodenum. These he designates as the pyloric gland system, as distinguished from the glands of the fundus, which secrete hydrochloric acid, pepsin and rennin. The author emphasizes, however, that one finding when first considered does not appear to be in accord with his theory. It does not introduce, however, an insurmountable difficulty to the acceptance of it. It is the fact that when the stomachs of patients with pernicious anemia are examined the histologic picture is just the reverse of what one would anticipate. In other words, anatomic studies show that the pyloric glands, which produce the intrinsic factor, are normal and that the abnormalities involve the glands of the fundus. Two suggestions are made to reconcile this fact with his theory. (1) The glands of the fundus may act as a starter, or pacemaker, for the pyloric gland system either through production of hydrochloric acid and pepsin or (perhaps) through a hormonal action or (2) the interaction between the intrinsic and extrinsic factors may occur mainly in the small intestine, where the changes resulting from achlorhydria may render conditions unfavorable for such a process. Both of these explanations are ingenious, logical and worthy of serious attention, but they are still unproved. The author is the first to admit this, in his statement that "there is still much work to be done in this field of investigation."

Another point to which considerable discussion is devoted is the rather confusing but correct information that the intestines have some anti-pernicious-anemia activity. This fact appears to be clearly established. A table taken from the work of the Finnish investigator Votila is given, which shows the relative potency of the various parts of the gastrointestinal tract. The following list is based on the assumed activity of the total stomach as 100

Cardia	30	Jejunum	24
Fundus	2	Ileum	44
Pylorus	120	Large intestine	9
Duodenum	35		

It is Meulengracht's tentative belief that the anti-pernicious-anemia activity of the intestines is due to the presence of the completed substance, of the liver factor or perhaps of an intermediate product. The observations of Castle support this view. He found that prolonged washing of the ileum removes its hemopoietic activity, which would lead one to consider that the principle is formed elsewhere and is merely absorbed by the intestinal wall rather than secreted by it. Meulengracht has observed also that the intestinal material possesses "a certain degree of thermostability," which would indicate that it is a different substance from the intrinsic factor secreted by the stomach, as the latter is easily destroyed by heat.

Kaufmann and Thiessen² studied the blood and the gastric secretions of 48 patients with pernicious anemia and 168 of their blood relatives in order to obtain an idea concerning the familial incidence of the disease and information concerning its mode of transmission. In 8 families, or 16.7 per cent, more than one member was found to have the disease, as follows: "once in twin females, once among three brothers and sisters, twice in mother and son, twice in brothers, once in brother and sister and once in cousins." The authors attribute the high incidence in their studies to (1) the fact that the relatives investigated had all reached the age when pernicious anemia commonly develops and (2) the fact that the hospitals (of Hamburg, Germany) had excellent records, which made it possible to trace the history of deceased relatives. The occurrence of anacidity in 1 parent in each of 3 cases investigated in which both parents were examined led them to conclude that pernicious anemia is transmitted as a dominant characteristic. They also conclude that in families there may be persons who do not have fully developed pernicious anemia but are "carriers" of the disease from a hereditary standpoint. These persons may have glossitis, atrophy of the papillae of the tongue and either anacidity or subacidity. The occurrence of essential hypochromic anemia in relatives of patients with pernicious anemia is observed too often for the association to be fortuitous. As the authors do not believe that the two diseases can have the same extrinsic cause, they conclude that they must have a common, inherited one. In support of this view they state that they have observed a patient with essential hypochromic anemia in whom pernicious anemia developed, which speaks for a pathogenic relation between the two diseases. The authors are in agreement with Castle that pernicious anemia is due to a diminution in secretion of the intrinsic factor, which they believe is an inherited dominant characteristic. It is emphasized, however, that this gastric deficiency can also be purely exogenous in origin but that such an origin is less important.

² Kaufmann, O., and Thiessen, K. Hereditary Biology of Pernicious Anemia, *Ztschr f klin Med* **136** 474, 1939.

Jahsman³ reviews the histories of 223 cases of pernicious anemia observed at the Henry Ford Hospital between 1926 and 1938. Some useful suggestions are made concerning therapy, which in his review are summarized under the title "Treatment of Pernicious Anemia." An idea of the incidence of the disease is given by the statement that there was an average of 2.2 cases of pernicious anemia for every thousand new admissions to the hospital during the period. The disease occurred with equal frequency in the two sexes, which is in accord with the current opinions concerning sex distribution. The age range was from 17 to 81 years, most of the patients were aged 40 or over. The interesting observation is made, with which we are in agreement, that there is an increasing number of patients in whom the disease develops while they are in the early thirties or even younger. In this group, for example, between 1926 and 1931, 10 per cent of the patients were under 40 years of age, 3 were under 30, the youngest being 29. In the new cases observed between 1931 and 1938, 18 per cent of the patients were under 40, 10 were under 35, 5 were under 30 and the youngest was 17. This tendency of a disease which is commonly considered to be limited to persons of middle age or older to occur in younger persons appears to obtain with pernicious anemia as well as with other diseases, such as coronary thrombosis. While this observation arouses considerable speculation, the real explanation is not apparent at present.

Davidson⁴ presents an admirable summary of the knowledge concerning the factors involved in production of the macrocytic anemias and emphasizes the main types with illustrative case histories. His review merits a careful reading by all workers in the field of hematology, the data are well epitomized, and some engagingly provocative statements are made. He considers that there are many types of macrocytic anemia which have in common only the fact that the average size of the erythrocyte is greater than normal. Otherwise they differ in causation, in response to treatment and in the blood picture. In general, however, they can be divided into two groups.

Group 1 consists of macrocytic anemias developing from megaloblastic bone marrow and consequent on a deficiency of a specific factor essential for the continuation of normal blood formation.

Group 2 consists of all macrocytic anemias which are due to a cause which differs from that mentioned. Such macrocytic anemias are relatively rare and result from widely differing causes. In a majority of cases, however, the macrocytosis is secondary to "prolonged stimulation or irritation of the bone marrow." Macrocytic anemias belonging

3 Jahsman, W. E. Prevalence of Pernicious Anemia. Review of Two Hundred and Twenty-Three Cases, *J. Michigan M. Soc.* **38** 405, 1939.

4 Davidson, L. S. P. The Mechanism of Megaloblastic Blood Formation, *Cambridge M. J.* **64** 474, 1939.

to group 2 are present (a) with some forms of hemolytic anemia, for example, acholuric jaundice, (b) occasionally in cases of malignant malaria and lead poisoning, (c) not infrequently in cases of aleukemic leukemia and the terminal stages of leukemia, and (d) in cases of Hodgkin's disease and malignant disease with metastasis to the bone marrow

The macrocytic anemias of group 2 may be differentiated from the true megalocytic anemias on three main grounds (1) by recognition of the cause, (2) by full examination of the blood picture, which differs in important details in regard to red blood cells, white blood cells and platelets, (3) by failure of the condition to respond to anti-pernicious-anemia medication, and (4) by the favorable effect of other measures, such as splenectomy and irradiation Davidson aptly remarks that "all megalocytic anemias are macrocytic, but all macrocytic anemias are not megalocytic"

The major portion of Davidson's communication deals primarily with the anemias which arise from megaloblastic blood formation The mechanism of this is discussed from the standpoint of Castle's hypothesis, with which the author is in agreement The views of the author regarding the causes of these various anemias may be summarized as follows

Pernicious anemia develops in patients who are born with stomachs which fail to secrete first hydrochloric acid, then enzymes and finally the intrinsic factor The name pernicious anemia should be reserved for the megaloblastic anemia which arises from a loss of intrinsic factor in association with a constitutional defect in gastric secretion The inability of the stomach to secrete hydrochloric acid and the intrinsic factor is permanent and irreversible, hence substitution therapy must be continued for life

Davidson believes that pernicious anemia of pregnancy develops in a woman who has a latent constitutional factor in the stomach which is made apparent by the increased demands of the mother and the fetus for the antianemia principle It is likewise consequent on lowering of gastric function, which constantly occurs during pregnancy Davidson intimates that possibly true pernicious anemia develops in such women twenty to thirty years after recovery from the pernicious anemia of pregnancy

It is believed that in extremely rare instances macrocytic anemia may arise when there is a temporary loss of the intrinsic factor due to prolonged dietary deficiency and chronic gastritis The author presents what he considers to be such a case, in which there was a "permanent cure" of the megalocytic anemia, with return of free hydrochloric acid in the gastric secretions and reappearance of the intrinsic factor as proved by the biologic test

Proof that macrocytic anemia may develop from a lack of the extrinsic factor is to be found in the occasional case in which the condition responds to oral ingestion of autolyzed yeast. While such a deficiency is rare in temperate climates, it is apparently common in the tropics. The characteristic features of tropical anemia are summarized by Davidson as follows. The blood picture is identical with that of true pernicious anemia, the amount of hydrochloric acid in the gastric secretions is usually normal, there is no increase in plasma bilirubin, lesions of the central nervous system never develop, and an excellent response to autolyzed yeast occurs. It is principally for the last reason that tropical macrocytic anemia has been regarded as a deficiency state due to lack of the extrinsic factor.

Megaloblastic blood formation may result from failure of absorption of the specific antianemia factor due to intestinal impermeability, diarrhea of mechanical causes, such as fistulas of the bowel or short-circuiting operations.

Macrocytic anemia may develop in patients with disease of the liver when there is failure of storage or of final synthesis of the antianemia factor in that organ. While this concept is accepted by Davidson, he does not believe that the defect in storage can be solely responsible for the anemia in some cases, because in them there is partial or complete failure to respond to parenteral liver therapy. It is possible in such instances that the liver may play some role in final elaboration of the antianemia product and that this function is injured in patients with disease of the liver. Or, the suggestion is made, the failure to respond may be due to injury to the bone marrow from the toxic products formed or retained as a result of failure of the liver.

Finally, the possibility of development of hyperchromic macrocytic anemia due to failure of the bone marrow to utilize the specific antianemia factor (achrestic anemia) is discussed by Davidson. He likewise considers the possibility that the absence of a favorable response to potent anti-pernicious-anemia therapy may be explained by exhaustion of the bone marrow (aplastic anemia). The final acceptance of the concept of achrestic anemia is held in abeyance, however, pending additional studies.

Schenken, Stasney and Hall⁵ report studies which are confirmatory of previous work indicating that the pyloric and prepyloric regions are a source of the "intrinsic factor." An extract was prepared from the liver of a patient whose death was due to carcinoma of the pyloric and prepyloric regions of the stomach. No data, however, are given which

5 Schenken, J. R., Stasney, J., and Hall, W. K. Lack of Antianemic Principle in Human Liver from Case of Carcinoma of Stomach, *Proc. Soc. Exper. Biol. & Med.* **40**: 89, 1939.

show that this patient had macrocytic anemia. The liver extract from this patient failed to produce a reticulocyte response, whereas a similar extract prepared from a patient who died from a cerebral hemorrhage was potent.

Brunschwig and his associates⁶ postulate that the achlorhydria invariably observed with pernicious anemia may be associated with the formation of some substance which, acting on the foveolar portions of the gastric glands or on the parietal cells themselves, leads to inhibition of the secretion of hydrochloric acid and its liberation as free acid. In order to study this problem, gastric juice obtained from patients with pernicious anemia was injected intravenously into dogs with gastric pouches. The changes in the gastric secretions collected from the pouches were noted after feeding. The authors observed a transitory marked depression of the secretion in the pouch and achlorhydria (89 per cent of the samples) when the gastric juice of 16 of 18 patients with pernicious anemia was injected intravenously. Injection of gastric juice from a group of patients who did not have pernicious anemia caused similar gastric secretory inhibition in only 18 per cent of the tests. It was determined that this secretory depressant effect of gastric juice is abolished by boiling for ten minutes. The authors interpret their observations as suggesting that the gastric secretory depressant found in relatively high concentration in the gastric juice of patients with pernicious anemia represents a marked increase of a factor that may be normally present in relatively low concentrations in the gastric secretions of patients who do not have pernicious anemia.

It is stated by Dexter and his co-workers⁷ that previous studies by various workers have demonstrated the effectiveness of preparations from the small intestines and colon of the hog in bringing about an increased production of blood in patients with pernicious anemia. Rather than conclude that this indicates a secretion of the intrinsic factor by the intestines as well as by the stomach, these observers consider that this blood-forming activity may be due entirely to passive adsorption of the intrinsic factor which is formed in the stomach. In support of this view they demonstrated that prolonged washing removed the hemopoietic activity of the lower half of the intestine, whereas a similar procedure had no effect on the stomach. Washing did not remove the activity of the duodenal mucosa, but mincing and then washing rendered it inactive, although similar treatment of stomach tissue

6 Brunschwig, A., Van Prohaska, J., Clarke, T. H., and Kandel, E. A Secretory Depressant in Gastric Juice of Patients with Pernicious Anemia, *J. Clin. Investigation* **18** 415, 1939.

7 Dexter, S. O., Heinle, R. W., Fox, H. J., and Castle, W. B. Basis of the Hematopoietic Activity in Pernicious Anemia of Desiccated Hog Ileum, *J. Clin. Investigation* **18** 473, 1939.

did not have the same effect. They demonstrated, furthermore, that the anti-pernicious-anemia effect of ileum is readily destroyed by boiling, which distinguishes it from the active thermostable principle in liver. It is suggested that the hemopoietic ability of the ileum of the hog is due to passive adsorption of gastric secretion. The authors are uncertain whether the activity of the washed duodenum is due to active secretion of the extrinsic factor or to the ineffectiveness of the washing process in eliminating higher local concentration of adsorbed intrinsic factor. These experiments are illuminating, but they are difficult to interpret, as so much depends on the differential effectiveness of "washing" in determining whether a material is secreted or absorbed by a tissue.

Further studies on liver are reported by Dakin and West,⁸ who attempt to determine the chemical identity of the active principle controlling the regeneration of blood in patients with pernicious anemia. They have previously shown that there is a substance in liver which has this effect, it is a peptide and in some respects resembles a typical albuminose. Karrer, Frei and Fritzsche⁹ report that the active substance is a biuret-negative peptide with an elementary structure which resembles the product isolated by Dakin and West. The present report of the latter two investigators shows that the liver material active in subjects with pernicious anemia is precipitated by typical albuminose precipitants, such as bile, taurocholic acid and nucleic acid. A further fact of additional interest is that the peptide which they have isolated is free from the nicotinic acid group.

Barker and Hummel¹⁰ give a review of the literature and report 2 new cases of macrocytic anemia associated with intestinal strictures and anastomoses. This article is abstracted in considerable detail because it discusses so thoroughly the entire problem regarding the relation of the macrocytic anemias to the intestinal tract and presents a novel theory concerning the cause of pernicious anemia. They state that the first instance of this association was recorded by Faber¹¹ in 1895. Since

8 Dakin, H. D., and West, R. Hematopoietic Substance in Liver, *Proc. Soc. Exper. Biol. & Med.* **40** 124, 1939.

9 Karrer, P., Frei, P., and Fritzsche, H. Ueber einen Bestandteil von gegen perniziöse Anämie hochaktiven Lebertraten, *Helvet. chim. acta* **20** 622, 1937. Karrer, P., Frei, P., and Ringier, B. H. Bestandteile von gegen perniziöse Anämie hochaktiven Lebertraten. II. *ibid.* **21** 314, 1938.

10 Barker, W. H., and Hummel, L. E. Macrocytic Anemia in Association with Intestinal Strictures and Anastomoses. Review of Literature and Report of Two New Cases, *Bull. Johns Hopkins Hosp.* **64** 215, 1939.

11 Faber, K. Pernicious Anemia Due to Intestinal Trouble, *Hospitalstid* **3** 601, 1895, Perniciöse Anämie bei Dunndarmstrikturen, *Berl. klin. Wchnschr.* **34** 653, 1897.

then, reviews by Meulengracht¹² in 1929 and by Hurst¹³ in 1933 have brought the number of recorded cases up to 39. The authors have collected 10 more cases from the literature and added 2 of their own, thus making a total of 51 cases for consideration.

In almost all such cases the symptoms are predominantly those of partial intestinal obstruction, namely, diarrhea or intermittent diarrhea and constipation, distention, abdominal cramps and, less frequently, nausea and vomiting. Usually there is marked loss of weight secondary to the gastrointestinal disturbances. Barker and Hummel state that the pathologic picture established by them at necropsy, by operation or by roentgen examination consisted of strictures of the large intestine in 7 cases, enteroenterostomy or enterocolostomy openings in 13, gastro-jejuno-colic fistula in 4 and gastro-colic fistula in 1. The majority of the strictures of the small intestine were located in the ileum, and of these about one half were definitely tuberculous in origin. Certain of the nontuberculous strictures were due to nonspecific terminal ileitis. Anastomosis of various types was the abnormality in about one third of the cases, and this was most frequently either an enteroenterostomy or an enterocolostomy resulting from surgical procedures which had been performed for the relief of intestinal obstruction.

Anemia of the pernicious type was present in all cases, and in some it was severe, as was indicated by a red blood cell count below 1,000,000 per cubic millimeter in 8 instances. Macrocytosis was specifically mentioned in a great majority of cases, a mean corpuscular volume of over 120 cubic microns was not unusual. Forty-seven per cent of the patients had free hydrochloric acid in the gastric juice, and it probably would have been detected in a larger percentage if the analyses had been made after injections of histamine. The presence of free hydrochloric acid in the gastric secretions of course sharply differentiates this type of macrocytic anemia from true pernicious anemia, which is always associated with achlorhydria. The intrinsic factor of Castle was tested for directly in only 2 cases. In 1 it was present, and in the other it was absent. The response to a diet rich in the extrinsic factor was interpreted as indirect evidence of absence of the intrinsic factor in 2 additional cases.

Studies of the ability of the body to absorb fat, dextrose and ascorbic acid were made in a few instances. It was concluded from the somewhat scanty available data that probably defective intestinal absorption alone cannot explain the development of macrocytic anemia in this group of patients. The paucity of the observations prevents definite acceptance

12 Meulengracht, E. Pernicious Anemia in Intestinal Stricture, *Acta med Scandinav* **72** 231, 1929.

13 Hurst, A. F. A Case of Addison's Anemia with Subacute Combined Degeneration of the Spinal Cord and Normal Gastric Secretion Following Chronic Obstruction of the Ileum, *Guy's Hosp Rep* **83** 47, 1933.

of this conclusion, but in our opinion such studies are exceedingly important and are worthy of further investigation. The authors concede that their information is inadequate and that only tentative conclusions can be drawn from it. They have not demonstrated conclusively that the patients fail to absorb the erythrocyte-maturing factor.

The patients were divided into four groups, depending on the type of treatment. Group 1 (23 patients) received supportive treatment for the most part, and 22 died, 3 of the patients who were placed on milk diets were temporarily benefited. This suggests to us that the protein of the milk, perhaps acting as the extrinsic factor, was the component responsible for the improvement in these patients. Group 2 included 9 patients who were treated by various surgical procedures, 5 died so soon after the operation that no conclusion could be drawn regarding the effect on the anemia. The 4 who survived showed striking symptomatic and hematologic improvement after operation. In 2 additional cases an ileocolostomy was performed to circumvent strictures of the terminal portion of the ileum. The immediate results were excellent, but sufficient data were not available to determine whether relapses occurred. The authors stress the fact that macrocytic anemia may develop after an anastomosis has been performed to circumvent strictures, which is important from the standpoint of practical therapeutic management. Group 3 was made up of 9 patients who were treated with liver alone. Six of these showed striking improvement, 3 of whom gave satisfactory responses to oral administration of liver preparations. The results observed in these 3 patients lead the authors to conclude that there was no marked disturbance of intestinal absorption in these cases. Group 4 included 10 patients who were unsuccessfully treated by surgical intervention and were then given liver therapy.

The conclusions drawn concerning various types of therapy for "stricture anemia" are as follows: 1. Without surgical or anti-pernicious-anemia therapy, the outlook for improvement is very poor. 2. A high operative mortality is associated with the surgical procedures employed to correct the intestinal abnormalities. 3. Elimination of the abnormal intestinal condition may or may not be followed by complete cure. 4. An anastomotic operation designed to circumvent a stricture is less likely to succeed than is resection of a stricture or restoration of the normal continuity of the bowel when an anastomosis is the offending lesion. 5. Although liver therapy may control the anemia, it cannot be expected to relieve the symptoms due to partial intestinal obstruction. 6. Surgical treatment is indicated for all patients with strictures and for young patients with anastomoses. 7. Liver therapy alone is indicated for older patients with well functioning anastomoses in whose cases the operative risk is great.

The authors do not believe that the condition of their patients represents a coincidental association of an intestinal lesion with addisonian pernicious anemia. This is because in a number of cases free hydrochloric acid was present in the gastric secretions, in a few there was evidence that the intrinsic factor of Castle was present in the gastric secretion and, finally, surgical correction of the lesion was followed by disappearance of the macrocytic anemia. Among other mechanisms which may have caused the macrocytic anemia is deficient absorption of the hemopoietic principle, such as occurs in cases of sprue. It is conceivable that enteritis due to stagnation occurring above strictures or in short-circuited loops may interfere with absorption of this substance. Evidence against this is furnished by data indicating that in some cases absorption of dextrose, fat and the active principle of liver was unimpaired. In some patients a deficiency of the extrinsic factor in the diet may play an etiologic role, if this is true, it is probably of secondary importance. It is not considered that extensive damage to the liver was important in the causation of anemia in these cases.

According to the authors, this leaves for consideration the possibility that excessive bacterial activity in the intestinal tract may have been the cause of the macrocytic anemia. Such a pathologic change could act (1) by preventing formation of the hemopoietic factor or destroying it or (2) by elaboration of an excessive amount of the "toxic products of bacterial putrefaction," which cannot be neutralized by the detoxifying mechanisms of the body.

Faber, in 1895, was the first to ascribe the macrocytic anemia associated with stricture of the small bowel to absorption of a toxin from the stagnant intestinal contents. Meulengracht in 1921 stated that such an anemia is probably due to absorption of "hematoxic substances" from the dilated and infected portion of the bowel above the stricture. Furthermore, in his opinion such a condition supports the theory of the intestinal origin of cryptogenic pernicious anemia. The experimental production of intestinal stricture in dogs, the treatment of "idiopathic" pernicious anemia by ileostomy and colonic irrigations and the study of pathologic flora in the gastrointestinal tract have all furnished suggestive evidence favoring the enterotoxic theory of pernicious anemia.

Even with the acceptance of Castle's work, which indicates that pernicious anemia is a deficiency disease or at least a "conditioned deficiency state," the authors maintain that the action of the liver principle is still far from clear. They suggest that there is evidence to support the contention that the liver principle may be necessary to promote proper detoxification of some chemical compound or compounds which, if unneutralized, might give rise to a variety of harmful changes through-

out the body. On this basis it may be assumed that the beneficial effects of liver therapy may be due to the ability of the liver principle to detoxify the excess of toxins absorbed from stagnating intestinal contents in subjects with strictures or anastomoses of the small intestine. If this hypothesis were applied to the development of addisonian pernicious anemia, it would be assumed that there is a failure of the body to synthesize the detoxifying principle in sufficient amounts to neutralize the toxic substance normally absorbed from the intestinal tract when stagnation is not necessarily a factor.

We have been interested for a number of years in the mechanism of production of macrocytic anemias associated with abnormalities of the small intestine. It appears to be clearly established that there is a causal relation and that the final proved explanation will provide important new information regarding the causation of the macrocytic anemias. Superficially, it is logical to assume that the anemias associated with intestinal anastomoses are due to a failure in normal absorption of the active principle of liver, although Baiker and Hummel appear to have accumulated some evidence against such an interpretation. The theory which has a bearing on the cause of the macrocytic anemia associated with intestinal strictures, although it may not be ultimately substantiated, is a rational one which should provoke further promising etiologic studies.

Alsted¹⁴ is in agreement with Castle and his collaborators that true addisonian pernicious anemia is due to a lack of "intrinsic factor," which is derived from the stomach. There is less adequate evidence, however, to prove that a similar condition can result exclusively from a lack of the "extrinsic factor" in the diet. We are in accord with the statement that in temperate climates cases of such a condition appear to be extremely rare, on the other hand, it is said that they occur more frequently in the tropics. A statement which seems applicable to the theories regarding the cause of the tropical macrocytic anemias is that "in the tropics conditions are difficult to gauge, it is often impossible to detect the single dietary deficiency causing anemia, and, furthermore, various infections may influence the aspect of the blood." Alsted reports 1 case of macrocytic anemia, stating that many facts make it highly likely that the anemia was due to a deficiency exclusively of the extrinsic factor in the food.

The patient, a man aged 43, had severe anemia (red blood cell count, 1,300,000 per cubic millimeter), a high color index, pronounced glossitis, the characteristic picture of pernicious anemia on sternal puncture and the classic Price-Jones distribution curve were present. Against the diagnosis were a normal icteric index and the presence of free acid in

14 Alsted, G. Exogenous Pernicious Anemia, *Am J M Sc* **197** 741, 1939

the gastric secretions. We note with interest, however, the complete absence of acroparesthesia, which in our experience is present in 90 per cent of patients with true Addisonian anemia. Thorough examination failed to disclose evidence of idiopathic steatorrhea, intestinal stricture, intestinal parasites, pellagra, syphilis, tuberculosis, chronic nephritis, Hodgkin's disease or any other of the diseases that are occasionally accompanied with macrocytic anemia. No specific mention is made, however, of the possibility of extensive disease of the liver or of the employment of tests of hepatic function. Some believe that macrocytic anemia can result from a pathologic change in this organ.

The patient had been on a restricted diet for seven or eight years, which was deficient in meat, eggs and milk. The author regards these substances as the chief sources of the "extrinsic factor." A minute dietary history disclosed that there was no deficiency of the known vitamins, although there was a lowered intake of calcium and phosphorus. According to the author, conclusive evidence of the lack of "extrinsic factor" was obtained when a complete remission, including a reticulocyte response, followed "treatment with nothing but 'extrinsic factor' and plenty of ordinary food." The patient remained well seven months later despite the fact that he did not take any medicine, merely continuing to consume a well balanced diet. It is of interest that there was complete restoration of the gastric secretion to normal. The suggestion is offered that a deficiency of the "extrinsic factor" causes achylia and that this in turn results in impaired absorption of the already scantily available extrinsic factor and of the eventually formed anti-anemia factor. The author concludes with the interesting speculative statement that "exogenous pernicious anemia" occurs more frequently than is generally believed. Its presence is obscured, however, because liver and stomach preparations are equally effective for the exogenous and the endogenous form.

The studies of Wintrobe¹⁵ on the anti-pernicious-anemia effect of yeast resulted from his observation that diets "supposedly" lacking in the "extrinsic" factor failed to produce macrocytic anemia in animals. In searching for the cause of failure of these experiments, he found in testing each constituent of the diet fed to the animals that brewers' yeast when given to a patient with pernicious anemia caused a well marked hemopoietic effect. Studies were then begun to determine (1) whether oral administration of yeast regularly causes a hemopoietic effect in patients with pernicious anemia, (2) whether the potency of yeast can be enhanced by preliminary mixing with gastric juice, (3) whether the antianemic effect of yeast is dependent on the persistence

¹⁵ Wintrobe, M. M. Antianemic Effect of Yeast, *Am J M Sc* **197** 286, 1939

of the intrinsic factor in the patient, and (4) the nature of the active substance in yeast and its relation to the antianemia principle contained in liver

An excellent review of the literature dealing with the effectiveness of yeast in the treatment of pernicious anemia is given. From this it is concluded that autolyzed yeast in amounts of 45 Gm or more daily was effective in about one third of the cases of pernicious anemia in which it was tested. Smaller doses were effective after incubation with gastric juice. It appears to have been assumed without adequate study that nonautolyzed yeast does not possess antianemia potency.

After studying the effect of nonautolyzed yeast on patients in relapse (in doses of 1 to 2 Gm per kilogram of body weight daily and a maintenance dose of 0.3 to 0.8 Gm per kilogram daily), it was concluded that dehydrated brewers' yeast given orally "may" cause a hemopoietic response in cases of pernicious anemia which is as great as that produced by oral administration of liver extract derived from a quantity of liver two to eight times the weight of the brewers' yeast used. In the opinion of the author, the effectiveness of yeast may be due to its high concentration of extrinsic factor. This may react with even a minute amount of intrinsic factor, which is known to be present in the gastric secretions of some patients with pernicious anemia. Another equally plausible explanation, however, is that the antianemia factor in yeast differs from that in beef muscle not only quantitatively but qualitatively. According to Wintrobe, this statement is supported by his observations that yeast resembles in its antianemia effect the factor or factors in liver and desiccated hog stomach when given orally. It is his opinion, furthermore, that since knowledge of the physiologic disturbance associated with pernicious anemia and of the chemical nature and mode of action of the "extrinsic," "intrinsic" and "antianemic" principles is imperfect, one is not justified in drawing conclusions concerning the nature of the antianemia material in yeast. There is no positive evidence that the yeast factor is one of the B vitamins. For this purpose, studies have also been made of sources of these vitamins other than yeast, which include observations on the hemopoietic effect of wheat embryo, egg white, rice polishings, riboflavin and nicotinic acid. It has not been demonstrated that there is a relation between any one of the B vitamins and the antianemia substance.

Wintrobe, Samter and Lisco¹⁶ have attempted to produce in young pigs a condition similar to pernicious anemia in man by giving a diet adequate in all respects except in some factor supplied by brewers' yeast

¹⁶ Wintrobe, M. M., Samter, M., and Lisco, H. Morphologic Changes in Blood of Pigs, Associated with Deficiency of Water-Soluble Vitamins and Other Substances Contained in Yeast, *Bull. Johns Hopkins Hosp.* **64**: 399, 1939.

Although anemia of variable severity and degree of macrocytosis appeared in the animals, the results were equivocal so far as production of the characteristic blood picture of pernicious anemia was concerned. The present studies confirm those made in 1938, in which a dietary deficiency was followed apparently by changes in the posterior columns of the spinal cord, the peripheral nerves and the "dorsal root ganglion cells"¹⁷. Although their observations do not disprove that thiamine, riboflavin and nicotinic acid have an effect on blood formation, the authors conclude that the anemia which they observed appeared to be due to some other component of yeast. In 4 animals with anemia produced by the method just described, yeast therapy was followed by reticulocytosis and partial or complete relief of the anemia. A purified liver extract had no effect, and a crude extract was used, likewise without result, but it is possible that an infection in the animal inhibited the response.

Heinle and Miller,¹⁸ after studying the response of patients with pernicious anemia to yeast, do not agree with Wintrobe and his associates¹⁷ that this material contains some hemopoietic factor specific for the disease. In 2 patients with pernicious anemia a reticulocyte response was obtained after the administration of dried brewers' yeast. This response was neither as great as that evoked with a minimal amount of ventriculin calculated to produce maximal reticulocytosis nor as great as that resulting from daily intramuscular injections of unconcentrated liver extract. It was considered by these observers that the response to yeast resulted from administration of an excess of extrinsic factor in the presence of greatly diminished but not completely absent intrinsic factor. It is their conclusion that the assumption that yeast contains a hemopoietic substance which is specific for pernicious anemia is unnecessary.

Foy and Kondi,¹⁹ in studying nutritional macrocytic anemia as seen in Macedonia, observed that it responds equally well to a highly concentrated liver extract and to less purified preparations. This work suggests that the conclusion of Wills and Evans (1938) and Napier (1939) that tropical macrocytic anemia as seen in India is not benefited by highly purified liver extracts does not apply to the type of nutritional anemia

17 Wintrobe, M. M., Mitchell, D. M., and Kolb, L. C. Sensory Neuron Degeneration in Vitamin Deficiency. Degeneration of Posterior Columns of Spinal Cord, Peripheral Nerves, and Dorsal Root Ganglion Cells in Young Pigs Fed Diet Containing Thiamin (B₁) and Riboflavin But Otherwise Deficient in Vitamin B Complex, *J. Exper. Med.* **68**: 207, 1938.

18 Heinle, R. W., and Miller, F. R. Yeast as Extrinsic Factor in Relation to Pernicious Anemia, *J. Clin. Investigation* **18**: 257, 1939.

19 Foy, H., and Kondi, A. Response of Nutritional Macrocytic Anaemia to Anahaemin, *Lancet* **2**: 360, 1939.

treated by Foy and Kondi. Furthermore, the condition in India differs in other respects, as a high indirect van den Bergh reaction is rare, and glossitis is common.

An investigation was made by Wigodsky, Richter and Ivy²⁰ to determine whether the fetal liver contains the anti-pernicious-anemia factor. According to them, it is likely that the fetus is entirely lacking in the extrinsic factor except for that present in the amniotic fluid and in the small amount of detritus which collects in the gastrointestinal tract. It is improbable, however, that either of these serves as a source of the extrinsic factor. Although these two statements may be correct, proof is not presented by the authors. Such an assumption seems somewhat risky to us, as the exact nature of the extrinsic factor is unknown at present. The prompt reticulocyte responses together with the return to normal blood pictures in 3 cases gave indisputable proof of the presence of the anti-pernicious-anemia principle in fetal bovine livers. Since it is assumed that the fetus is completely lacking in the extrinsic factor, it is suggested that the anti-pernicious-anemia principle is conveyed to the fetal liver by passing from the circulation of the mother through the placenta into the fetal circulation. This conclusion is in accord with the view that withdrawal of the anti-pernicious-anemia principle by the fetus may be one cause of the macrocytic anemia of pregnancy. It is interesting to note that there is a variance between the results observed by these authors after administering bovine liver and those obtained by Wintrobe, Kinsey, Blount and Trager,²¹ who concluded that extracts of fetal swine liver were without effect when administered to patients with pernicious anemia. The authors are unable to account for this difference in results but suggest that (1) there may be a difference in permeability of the placenta of the pig and that of the cow or (2) the liver factor which is effective in the treatment of pernicious anemia is not required by the fetus for the maturation of red blood cells. This suggestion receives some support from the observation of Ivy and others that the injection of potent liver extract into pregnant rats and rabbits failed to reduce the size of the red blood cells of the newborn. It should be noted, however, that Stasney, Higgins and Mann²² have demonstrated that a concentrate of normal human or

20 Wigodsky, H. S., Richter, O., and Ivy, A. C. Presence of Anti-Pernicious Anemia Factor in Extract of Fetal Bovine Livers, *Am J M Sc* **197** 750, 1939.

21 Wintrobe, M. M., Kinsey, R. E., Blount, R. E., and Trager, W. Studies of Blood Formation in the Fetus and Newborn. III. Relation of Anti-Anemic Principle, Assay of Fetal Liver and Placental Extracts in Cases of Pernicious Anemia and in Mosquito Larvae, *Am J M Sc* **193** 449, 1937.

22 Stasney, J., Higgins, G. M., and Mann, F. C. Effect on Developing Red Blood Cells in Fetus of Administering Human and Hog Gastric Juice to Adult Rat During Pregnancy, *Am J M Sc* **197** 690, 1939.

swine gastric juice injected intraperitoneally into pregnant rats reduced the diameters of the red blood cells in newborn pups

Stasney, Higgins and Mann²² have employed the novel method of observing the effect of anti-pernicious-anemia substances in the physiologic macrocytosis of fetal white rats as a test for the principles governing hemopoiesis. This is based on the suggestion of Wintrobe and Schumacher that the macrocytosis observed in patients with pernicious anemia and that observed in fetal blood may both result from an inadequate amount of the essential antianemia principle. The technic used in the present investigation was to study the effect on the erythrocytes in young rats at birth of injecting concentrated normal gastric juice of man and swine into pregnant rats. The authors discovered that both human and swine gastric juices contain a substance which when injected into the pregnant adult rat accelerates the reduction in size and volume of the developing red blood cells of the newborn rat. Furthermore, it is concluded that these changes in the erythrocytes are proportional to the amount of gastric juice given to the adult rat during pregnancy and that the active substance is thermolabile. As a result of these experiments the authors suggest that the physiologic macrocytosis which occurs normally in the mammalian fetus may be due to an inadequate amount of the antianemia principle provided by the mother. The possibility that this effect on the fetal red blood cells may be utilized as a method of assaying the potency of the antianemia principle is considered. It is stated that the reaction is definite and that the extent of the decrease in size of the cells bears a direct relation to the amount of the principle administered. Additional study, however, is desirable in order to evaluate their method of bioassay.

In cases of untreated pernicious anemia, Schindler and Serby²³ by means of the gastroscope observed superficial gastritis, superficial gastritis plus atrophic gastritis and patchy or diffuse atrophy. After treatment the pathologic process persisted, disappeared or progressed. These authors confirm the previous observations of others that mucosal polyps are frequently present in the stomachs of patients with pernicious anemia.

A case of pernicious anemia unassociated with achlorhydria is reported by Finney²⁴. From the description it seems likely that hepatic disease was present.

Statistical data on the incidence of symptoms in 580 patients with pernicious anemia are given by Isaacs²⁵. Of these, ease of fatigue was

23 Schindler, R, and Serby, A. M. Gastroscopic Observations in Pernicious Anemia, *Arch Int Med* **63** 334 (Feb) 1939

24 Finney, J. O. Pernicious Anemia Unassociated with Achlorhydria, *Ann Int Med* **12**:1521, 1939

25 Isaacs, R. Diagnosis and Treatment of Pernicious Anemia, *J Indiana M A* **32** 607, 1939

outstanding in 85.1 per cent, numbness, in 81.2 per cent, tingling of the fingers and toes, in 74.3 per cent, shortness of breath, in 64.3 per cent, symptoms referable to the stomach, in 62.6 per cent, constipation, in 54.3 per cent, palpitation, in 49.3 per cent, edema, in 43.9 per cent, loss of appetite, in 43.9 per cent, difficulty in walking, in 43.6 per cent, symptoms referable to the bladder, in 35.0 per cent, dizziness, in 27.9 per cent, poor memory, in 26.8 per cent, diarrhea, in 26.5 per cent, pain, in 20.3 per cent, and stiffness, in 12.2 per cent. In most of the patients the disease developed between the ages of 35 and 65 years, with the peak of the distribution curve at 55 years. It appeared with equal frequency in the two sexes. The average length of the ear for the men was 7 cm. and for the women 6.5 cm., as compared with 6.7 and 6.1 cm. respectively for the general population. For treatment, 2 to 5 units of an antianemia medicament per day is recommended for very sick persons, with a maintenance dose of usually not less than 1 unit a day. Basophilia of the granules of the neutrophils, indicating pyogenic infection, calls for an increase to 3 to 5 units a day. Moore, Arrowsmith, Welch and Minnich²⁶ found that with patients with Addisonian pernicious anemia in relapse there was no demonstrable increase in the elevated values for serum iron when ferrous salts were given orally. However, after a remission induced by administration of liver normal absorption curves were noted, suggesting the possibility of selective absorption or rejection of iron by the mucosa of the intestine, depending on the state of the tissues.

Jacobson²⁷ suggests that the argentaffin cells of the stomach are possibly the ones which secrete the antianemia enzyme. They are located in the places where the enzyme is secreted, and they are absent or greatly reduced in number in cases of pernicious anemia and sprue. Their number was not observed by Jacobson to be diminished in cases of "secondary anemia" or of macrocytic anemia not responding to liver extract.

Berlin²⁸ found that during a relapse the blood of a patient with pernicious anemia contains less hemolytically active lysocithin than does normal serum. This probably results from the reduced function or lack of lecithinase, which the lysocithin forms from the serum lecithin. During remission the level of blood lysocithin returns to normal.

26 Moore, C. V., Arrowsmith, W. R., Welch, J., and Minnich, V. Studies in Iron Transportation and Metabolism. IV. Observations on the Absorption of Iron from the Gastro-Intestinal Tract, *J. Clin. Investigation* **18** 533, 1939.

27 Jacobson, W. The Argentaffin Cells and Pernicious Anaemia, *J. Path. & Bact.* **49** 1, 1939.

28 Berlin, R. Ueber die Herabsetzung des Hamolysingehalts und das Fehlen der spontanen Hamolysinbildung im Serum bei Anaemia perniciosa, *Acta med. Scandinav.* **98** 425, 1939.

Bruner²⁹ found that the leukocytosis following injection of liver extract is not specific for the anti-pernicious-anemia factor. The leukocytosis is not due to active granulopoiesis but to a redistribution in the capillary bed.

Schultz³⁰ found high concentrations of glutathione in the erythrocytes of patients with pernicious anemia or with myelogenous leukemia. With the former condition there was a drop in both the total concentration of glutathione and the oxidized fraction after treatment, which induced considerable clinical improvement without causing the red blood cell volume to reach normal.

While sodium nucleinate and pentose nucleotide induce peripheral leukocytosis with hastened maturation of granulocytes in the marrow, Nordenson³¹ found that this reaction does not take place in cases of infection or of pernicious anemia.

Veer³² feels that the red precursor of melanin may be of importance as an antianemia principle in cases of pernicious anemia and that pre-melanin may play a part in hemopoiesis.

Sturgis,³³ in an analysis of the cause of death of 147 patients with pernicious anemia (90 men and 57 women), found that only 32 per cent died of lesions directly associated with pernicious anemia, these were mostly complications referable to the spinal cord. Involvement of the central nervous system and complications referable to the bladder indicated an unfavorable prognosis. Of the deaths not due to pernicious anemia, heart disease, cancer, apoplexy, pneumonia, trauma and nephritis were prominent causes. At the end of three years, 63 per cent of the treated patients were alive (as compared with 24 per cent in Cabot's 1915 summary), and 35 per cent were still living at the end of five years (Cabot's series, 11 per cent).

High values for blood magnesium characterize pernicious anemia in relapse, but Bang and Ørskov³⁴ found that normal values were present during remission. On the basis of the magnesium studies the authors conclude that in pernicious anemia there is a short life of the

29 Bruner, H. D. Leukocytosis Following Parenteral Administration of Liver Extract in Man, *Am J Physiol* **127** 58, 1939.

30 Schultz, M. P. The Concentration of Glutathione in the Erythrocytes of Patients with Rheumatic Fever, *Pub Health Rep* **54** 264, 1939.

31 Nordenson, N. G. Experimental Leucocytosis in Man, *Quart J Med* **8** 311, 1939.

32 Veer, W. L. C. Melanin et ses precurseurs, *Rec d trav chim d Pays-Bas* **58** 949, 1939.

33 Sturgis, C. C. An Analysis of the Causes of Death in One Hundred and Fifty Fatal Cases of Pernicious Anemia Observed Since 1927, *Tr A Am Physicians* **54** 46, 1939.

34 Bang, O., and Ørskov, S. L. The Magnesium Content of the Erythrocytes in Pernicious and Some Other Anemias, *J Clin Investigation* **18** 497, 1939.

red blood cells with an increased rate of destruction. Remission is the result of stabilization of the red blood cells.

Pennetti³⁵ found that while the oxalic acid content of the blood in cases of hypochromic anemia and of the anemia of hemorrhage is within normal limits, in cases of pernicious anemia, of hepatic insufficiency and of phenylhydrazine anemia it is increased.

In patients with anemia, Ellis and Faulkner³⁶ found common circulatory characteristics to be cardiac enlargement, systolic murmurs, lowering of the systolic and diastolic pressures and abnormal electrocardiographic records (depression of the S-T segment and flattening or inversion of the T waves in lead I or in leads I and II). After treatment, as in cases of pernicious anemia, many of these abnormalities disappear or become less marked.

Cotti³⁷ reports that in cases of hemolytic icterus and pernicious anemia there is an increase in the excretion of porphyrin which appears to be independent of the amount of hemolysis.

In order to develop a formula which would represent reticulocyte production in terms of the time necessary to complete the reticulocyte response, Friedman, Isaacs and Lufkin³⁸ found the "average daily reticulocyte per cent." This figure which increases with the decrease in the erythrocyte count on the day that treatment was started (E_0), is expressed by the formula $\frac{20.2 - 4.1 E_0}{1 + 0.25 E_0}$. It takes into account the varying periods required in different cases to complete the "reticulocyte response."

Paddock and Smith³⁹ found that the thrombopenia associated with pernicious anemia in relapse is not a differentiating feature from other macrocytic anemias. After therapy the increase of platelets is parallel to that of erythrocytes.

Patrassi and Crepet⁴⁰ describe a patient with splenomegaly and hyperchromic anemia of the pernicious anemia type in whose case hepato-

35 Pennetti, G. Metabolismo dell' acido ossalico ed emopatie, *Haematologica* **20** 153, 1939.

36 Ellis, L. B., and Faulkner, J. M. The Heart in Anemia, *New England J. Med.* **220** 943, 1939.

37 Cotti, L. Ricambio emoglobinico e ricambio porfirinico in condizioni anemiche con particolare riguardo all'anemia perniciosa. Nota preliminare, *Boll. Soc. ital. biol. sper.* **14** 710, 1939.

38 Friedman, A., Isaacs, R., and Lufkin, A. "The Average Daily Reticulocyte Response" During Therapy in Pernicious Anemia, *J. Lab. & Clin. Med.* **24** 677, 1939.

39 Paddock, F. K., and Smith, K. E. The Platelets in Pernicious Anemia, with a Review of the Literature, *Am. J. M. Sc.* **198** 372, 1939.

40 Patrassi, G., and Crepet, M. Sulle reticolo-endoteliosi ad orientamento megaloblastico (splenomegalia pernicioso-emolitica e leucemia monocitica a screezio eritremico), *Haematologica* **20** 301, 1939.

therapy gave mediocre results, while splenectomy was followed by improvement. Similar cases in the literature are classed according to the prevalence of one of the component factors, such as hemolytic icterus. Even after disappearance of the collateral symptoms (achylia, glossitis) the disease continues to resemble pernicious anemia. Histologic studies of the spleen as well as of an enlarged axillary lymph node in the authors' case revealed hyperplastic reticuloendotheliosis localized predominantly or exclusively in the spleen, on which depended the myeloblastic transformation and the hyperhemolytic syndrome. These conclusions agree with the interpretation of pernicious anemia as a form of hemohistiocytosis (Feirata). Patrassi and Ciepet consider that megaloblastosis may be considered a sign of activation of the reticuloendothelial system and may be compared with the various systemic hematopathies, with more or less marked participation of the reticuloendothelial system.

Middleton and Wakerlin,⁴¹ in studying the effect of liver extract on *Paramecium*, found that it did not change the rate of fission significantly. In high concentration and with inactivated liver extract the rate of fission was delayed.

Tschesche and Wolf⁴² prepared an active liver extract, of which 40 mg was a sufficient maintenance dose for a patient for four weeks after injection. There was little or no biuret reaction, and a ninhydrin reaction occurred before and after hydrolysis. The material was a white powder giving a slightly colored solution. The composition was carbon, 50 per cent, hydrogen, 7 per cent, nitrogen, 14.5 per cent, and sulfur, 0.6 per cent. The substance is precipitated by Reinecke's acid, by rhodanic acid and by one-half to two-thirds saturation with ammonium sulfate. It does not dialyze through heavy parchment. The Molisch, Millon, acriflavine, purine, pterine, reduced sugar and phosphoric ester reactions are negative.

Murphy and Howard⁴³ report the almost unique experience of being able to maintain 133 patients with pernicious anemia at an erythrocyte level of 5,000,000 per cubic millimeter by intramuscular injection of a liver extract at average intervals of three and seven-tenths weeks and at intervals of three and six-tenths weeks with a more concentrated extract. They found that neither sex nor age definitely influences the

41 Middleton, A. R., and Wakerlin, G. E. Effect of Patenteral Liver Extract on the Fission Rate of *Paramecium Caudatum*, *Proc. Soc. Exper. Biol. & Med.* **42**: 442, 1939.

42 Tschesche, R., and Wolf, H. J. Ueber den Wirkstoff der Leber gegen perniziöse Anämie, *Naturwissenschaften* **27**: 176, 1939.

43 Murphy, W. P., and Howard, I. Use of Concentrated Liver Extracts in Pernicious Anemia. Survey of Maintenance Treatment of One Hundred and Seventy-Six Patients Under Continuous Observation for from Six Months to Six and One-Half Years, *J. A. M. A.* **112**: 106 (Jan. 14) 1939.

amount of anti-pernicious-anemia substance necessary for maintenance, although 27 patients above 70 years of age required injections at intervals of two and four-tenths weeks to maintain an average red blood cell count of 4,590,000 per cubic millimeter, as compared with 5 patients younger than 39 years who required injection at intervals of four and one-tenth weeks to maintain a red blood cell count of 5,250,000. "Treatment," they conclude, "should be individualized according to each patient's needs, determined on the basis of the patient's clinical condition and erythrocyte counts made at desirable intervals."

In the early treatment of pernicious anemia, Jahsman³ gives 195 U S P units parenterally the first week, 45 units the second week and 15 units each week thereafter until the red blood cell count reaches 4,500,000 per cubic millimeter, which usually requires six to eight weeks. The maintenance dose recommended by Jahsman is 15 units twice a month. Larger doses are required when infection is present. Adequate liver therapy will prevent the development or progress of changes in the spinal cord, but when changes in the central nervous system are marked, large doses of liver extract are needed. Jahsman feels that iron, dilute hydrochloric acid, vitamin medication, physical therapy and blood transfusions have a definite place in certain cases and at the proper time. Vitamin B₁ or vitamin B₂ proved to be valuable in treating the neural lesions associated with pernicious anemia when given parenterally in doses of 2 mg for thirty injections and of 10 mg for twenty-four injections in a three month period by Mussio-Fournier and Rawak.⁴⁴ The treatment was effective even after five or six years of the disease, and amelioration of the nervous symptoms appeared even before the blood had returned to normal.

In subjects with pernicious anemia the bone marrow of the femur was found by Keilhack⁴⁵ to have normal amounts of "protein" but an excess of "albumin."

Jones⁴⁶ describes the reactions of 2 Negro patients to injections of liver extract. The first showed urticaria after the injections, the second, a reaction involving the vascular, gastrointestinal and respiratory apparatus. Cutaneous reactions and reactions to the liver extract were demonstrated. Such sensitivity disappears after a time, and desensitization is possible. For this type of patient it may be necessary to change the therapy or the route of administration (oral).

44 Mussio-Fournier, J. C., and Rawak, F. Action thérapeutique de la vitamine B, dans la myélose funiculaire de l'anémie pernicieuse, *Rev neurol* **70** 604, 1938.

45 Keilhack, H. Ueber das Eiweiss im normalen und pathologisch veränderten Knochenmark des Menschen, *Deutsches Arch f klin Med* **182** 57, 1938.

46 Jones, C. A. Allergic Reactions Following Parenteral Administration of Liver Extract, *Internat Clin* **3** 258, 1939.

Wilkinson⁴⁷ describes a case of pernicious anemia in a man 26 years of age with neurologic involvement. There was a rapid response to liver extract and vitamin B₁. The patient's mother also had pernicious anemia, but there were no neurologic symptoms.

Central Nervous System—Neuropathic symptoms and signs occur in more than 80 per cent of patients with pernicious anemia. Wooster-Drought and Shafar⁴⁸ point out that the peripheral neuritis may be associated with other types of anemia and is probably due to a vitamin deficiency. Van Baalen and Vroon⁴⁹ cite several cases of pernicious anemia to demonstrate the various psychic changes which may occur. They observed marked mental improvement with elimination of the anemia. It should not be forgotten, however, that psychosis in a case of pernicious anemia may also be due to toxic effects from dysfunction of the genitourinary tract, cerebral arteriosclerosis and cerebral pathologic changes similar to those observed in the posterior and lateral columns of the cord.

Twenty patients with a paralytic form of involvement of the central nervous system were observed by Rosenthal and Abel⁵⁰. In the majority of instances prolonged and adequate antianemia therapy was effective in arresting, retarding, improving or preventing aggravation of the neuropathic symptoms. These investigators state that after adequate treatment with liver or potent liver extract they did not observe any recurrences or progression of symptoms.

In an effort to determine the cause of the degenerative changes in the cord associated with pernicious anemia, Wintrobe and his colleagues⁵¹ performed several experiments on young pigs. These animals were put on a balanced diet with large amounts of yeast. The yeast was gradually reduced and replaced by thiamine, riboflavin and nicotinic acid. These substances were given alone or in various combinations. All the animals which received reduced amounts of yeast had ataxia. Definite pathologic change was noted in the posterior columns and in the sensory nerves. Whether the results of these experiments can be

47 Wilkinson, J. N. Pernicious Anemia with Cord Involvement in a Young Adult. Case Report, *Clin Virginia Mason Hosp* **18** 19, 1939.

48 Wooster-Drought, C., and Shafar, J. Achlorhydric Hypochromic Anemia Associated with Peripheral Neuritis, *Brit M J* **2** 273, 1939.

49 Van Baalen, J., and Vroon, M. P. Mental Disorders in Pernicious Anemia, *Nederl tijdschr v geneesk* **83** 270, 1939.

50 Rosenthal, N., and Abel, H. A. Observations on the Effects of Liver Extract in Pernicious Anemia, with Special Reference to the Paralytic Form of Subacute Combined Sclerosis, *J Mt Sinai Hosp* **5** 349, 1938.

51 Wintrobe, M. M., Samter, M., and Lisco, H. Changes in the Blood and Nervous System of Pigs Associated with Deficiency of Substances Contained in Yeast, *J Clin Investigation* **18** 494, 1939.

utilized to explain the changes in the spinal cord associated with pernicious anemia is debatable, as many patients with pernicious anemia have involvement of the lateral as well as of the posterior column

GASTRIC JUICE AND THE ANEMIAS

The role of gastric juice in erythropoiesis and the importance of this function have been recognized for several years. Leroux and Vermes⁵² discuss in detail the various types of anemia associated with interference with normal gastric secretion. In their opinion there are multiple exogenous and endogenous factors, and the anemia is dependent on the effectiveness and combination of the factors which predominate. Dhayagude and Khadlihar⁵³ studied the relation of true achlorhydria and anemia. In 39 patients with anemia there was absence of "free hydrochloric acid" in the gastric contents after stimulation with histamine. The authors compared the results of a single fractional test meal and histamine stimulation. They concluded that the latter test gives more reliable information and that little, if any, risk is attached to it. In their series of cases achlorhydria was usually associated with pernicious anemia, Witt's anemia, ankylostomiasis and pellagra.

In an effort to determine the nature of the hemopoietic activity of gastric juice, Heinle and Miller⁵⁴ prepared gastric juice for parenteral therapy. When the extracts were given intravenously to 2 patients with pernicious anemia in relapse, no response was observed in either. The authors concluded that the gastric juice alone was ineffective because there was no extrinsic factor in the parenteral tissues to provide a substrate for interaction.

Brunschwig and his co-workers⁶ demonstrated the presence of a secretory depressant in the gastric contents of patients with pernicious anemia (see section on pernicious anemia).

The effect of normal and abnormal human gastric juice administered to the mother on the blood of newborn rats has been investigated by Schlicke⁵⁵. He noted an acceleration of hemopoiesis in the fetus, indicated by an increase in the number of red blood cells in the circulating blood, and a decrease in the volume and diameter of the fetal red blood cells at birth. The erythropoietic substance, which he observed to be

52 Leroux, R., and Vermes, E. Anemias "agastriques," *Sang* **13** 241, 1939.

53 Dhayagude, R. G., and Khadlihar, V. N. True Achlorhydria and Anaemia, *Indian J. M. Research* **26** 705, 1939.

54 Heinle, R. W., and Miller, F. R. Negative Effect of Gastric Juice Administered Intravenously to Patients with Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **40** 681, 1939.

55 Schlicke, C. P. The Effect of Normal and Abnormal Human Gastric Juice, Administered to the Mother, on the Blood of Newborn Rats. Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **14** 145, 1939.

present in variable amounts in normal human gastric secretions, was absent in the gastric contents of patients with pernicious anemia. He states that this substance is similar to the intrinsic factor of Castle, inasmuch as it can be inactivated by heating. Stasney, Higgins and Mann⁵² report somewhat similar experiments. In addition to human gastric juice, they employed pig gastric juice. In the opinion of these authors the resulting erythropoietic changes are proportional to the amount of gastric juice injected into the mother. Since the results are so constant, it has been suggested that this method may be satisfactory for assaying the potency of antianemia material.

Von Bonsdorff⁵⁶ exposed liver extract in vitro to the effects of fresh tapeworm, *Taenia saginata*, *Ascaris lumbricoides*, boiled tapeworm and alcoholic extracts of the tapeworm and of the colon bacillus. The extract was then given to several patients with pernicious anemia in relapse. The expected reticulocyte response was obtained. The influence of the intestinal worms on the proteolytic activity in vitro of trypsin, papain, pepsin and human gastric juice was also investigated by von Bonsdorff⁵⁶. His conclusions are most interesting. The aqueous extracts of the various worms had a definite inhibiting effect on the proteolytic activity of gastric juice on casein at a neutral p_H . The same extracts did not inhibit the action of trypsin, pepsin or gastric juice at a low p_H , on the contrary, hydrolysis, expressed as increased nitrogen in trichloroacetic filtrates, was more marked in digests containing worm emulsion. The worm proteins were quickly digested by trypsin, pepsin and papain but not by gastric juice at a p_H of 7.4. The addition of a broth culture of *Bacillus coli* did not noticeably affect the proteolytic activity of the enzymes or of the gastric juice at a neutral reaction. Tapeworms had considerable proteolytic effect on casein at a p_H of 7.4. This digestive process decreased quickly at a lower p_H and more slowly at a higher p_H . Within the range of neutrality and slight alkalinity there is auto-digestion of the worm. The author suggests the possibility that the worm enzyme and cathepsin are identical.

MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA

The pathologic physiology of the macrocytic anemias has been adequately reviewed by Rhoads,⁵⁷ Castle,⁵⁸ Benhamou,⁵⁹ Goodwin,⁶⁰

⁵⁶ von Bonsdorff, B. Liver Extract Exposed to the Action of Intestinal Worms Does Not Lose Its Anti-Anemic Effect, *Acta med Scandinav* **100** 436, 1939, The Influence of Intestinal Worms on the Proteolytic Activity in Vitro of Trypsin, Papain and Especially of Human Gastric Juice at Neutral Reaction, *ibid* **100** 459, 1939.

⁵⁷ Rhoads, C. P. Vitamins. Vitamin B₁₂ Therapy, *Conferences on Therapy, J A M A* **113** 297 (July 22) 1939.

Davidson,⁶¹ Blum⁶² and Wintrobe⁶³ It is a generally accepted fact that food (extrinsic factor) interacts with gastric juice (intrinsic factor) to produce the erythrocyte-maturing substance. This product is absorbed in the intestine, stored in the liver and released to the bone marrow as needed. Any interference in this chain of events results in macrocytic anemia.

Onhauser and Mitchell⁶⁴ describe a case of pernicious anemia of pregnancy. The hematologic diagnosis was based on the presence of a megaloblastic marrow. It is the opinion of these authors that, since the patient had an adequate diet, the anemia was the result of a deficiency of the intrinsic factor. This view is directly opposed to that of Goldhamer, Fitzell and MacKinnon,⁶⁵ who produced a remission in a patient with pernicious anemia of pregnancy by feeding a high protein diet (extrinsic factor). Ritter and Crocker⁶⁶ describe a third case of macrocytic anemia in pregnancy, with a similar type of anemia in the newborn infant. From the results of their experiments with fetal bovine livers, Wigodsky and his co-workers²⁰ suggest that pernicious anemia of pregnancy is probably due to removal of too much of the erythrocyte-maturing factor from the mother by the fetus.

Red blood cell fragility in 40 patients with tropical macrocytic anemia was studied by Evans and Wills⁶⁷. The median corpuscular fragility represented the concentration of salt solution which produced 50 per cent hemolysis. An analysis of their results revealed that in "complicated cases" of tropical macrocytic anemia there is increased fragility of the red blood cells, a fact which often masks the decreased fragility present in cases in which no complications occur.

58 Castle, W. B. The Diagnosis and Treatment of Anemia, Tr & Stud Coll Physicians, Philadelphia 7 129, 1939

59 Benhamou, E. Le traitement des anémies macrocytiques non bémériennes, Presse méd 47 755, 1939

60 Goodwin, R. Q. Macrocytic Anemias, South M J 32 641, 1939

61 Davidson, L. S. P. The Mechanism of Megoblastic Blood Formation, Edinburgh M J 46 474, 1939

62 Blum, L. L. Newer Concepts in the Interpretation of Anemias, J Indiana M A 32 120, 1939

63 Wintrobe, M. M. The Choice of Methods for the Collection of Anemia Internat Clin 2 44, 1939

64 Onhauser, V. F., and Mitchell, R. A Case of Pernicious Anemia of Pregnancy, Canad M A J 41 67, 1939

65 Goldhamer, S. M., Fritzell, A. I., and MacKinnon, F. The Role of the Protein Level Intake in the Production of Remissions in Macrocytic Anemias, J Clin Investigation 18 481, 1939

66 Ritter, J. A., and Crocker, W. J. Macrocytic Anemia of Pregnancy and Anemia of the Newborn, Am J Obst & Gynec 38 239, 1939

67 Evans, B. F. D., and Wills, L. Red Cell Fragility in Tropical Macrocytic Anaemia, J Path & Bact 48 437, 1939

Eight monkeys were observed after gastrectomy by Bussabarger and his co-workers⁶⁸ for two to three years. None had macrocytic anemia. Bachrach and Fogelson,⁶⁹ using dogs, removed seven-eighths of the stomach, all of the duodenum and 30 cm of the jejunum. Macrocytic anemia was never noted. The authors conclude that hemopoiesis in dogs may be different from that in man or that there may be some factor other than that in the stomach or the duodenum which is essential for erythropoiesis.

Ten patients with macrocytic anemia associated with various lesions of the bowel were observed by Sturgis and Goldhamer.⁷⁰ Brock⁷¹ also reports the occurrence of megalocytic anemia in patients with intestinal strictures. He considers that a multiple deficiency was present as a result of faulty absorption. Nontropical sprue complicated by anemia is reported by Frostad⁷² and Rodriguez-Molina.⁷³ In the series of cases analyzed by Rodriguez-Molina, macrocytic anemia was present in 90 per cent of the patients, normocytic anemia in 7 per cent, simple microcytic anemia in 1 per cent and hypochromic anemia in 2 per cent.

Macrocytic anemia due to disease of the liver from various causes is reported by Burgess and Maclaren,⁷⁴ by Townsend and Braunstein⁷⁵ and in a discussion of a Cabot case.⁷⁶ A most unusual series of experiments was performed by Sydenstricker and his colleagues⁷⁷ with liver extract prepared from a pellagrin. When this extract was administered parenterally to a patient with pernicious anemia a prompt response was obtained. Pellagrins treated with a similar extract failed to respond but

68 Bussabarger, R. A., Ivy, A. C., Wigodsky, H. S., and Gunn, F. D. The Effect of Gastrectomy on the Monkey, *Ann Int Med* **13** 1028, 1939.

69 Bachrach, W. H., and Fogelson, S. J. The Role of the Upper Gastrointestinal Tract in the Etiology of Pernicious Anemia, *J Lab & Clin Med* **24** 249, 1938.

70 Sturgis, C. C., and Goldhamer, S. M. Macrocytic Anemia, Other Than Pernicious Anemia, Associated with Lesions of the Gastrointestinal Tract, *Ann Int Med* **12** 1245, 1939.

71 Brock, J. F. Intestinal Stricture and Megalocytic Anaemia, *Lancet* **1** 72, 1939.

72 Frostad, S. A Case of Non-Tropic Sprue with Normo- and Megaloblasts in the Peripheral Blood, *Acta med Scandinav* **99** 257, 1939.

73 Rodriguez-Molina, R. Hematology of Sprue. Report on One Hundred Cases in Puerto Rico, *Puerto Rico J Pub Health & Trop Med* **15** 89, 1939.

74 Burgess, N., and Maclaren, C. A Case of Pigmented Eczema with Macrocytic Anaemia, *Brit J Dermat* **51** 207, 1939.

75 Townsend, S. R., and Braunstein, A. L. Hyperchromic Macrocytic Anemia in Association with Hodgkin's Disease, *Canad M A J* **41** 254, 1939.

76 Carcinoma of Pancreas with Metastases to Liver, Pernicious Anemia, Cabot Case 25232, *New England J Med* **220** 967, 1939.

77 Sydenstricker, V. P., Schmidt, H. L., Jr., Geeslin, L. E., and Weaver, J. W. The Liver in Pellagra, *Am J M Sc* **197** 755, 1939.

subsequently showed improvement when commercial liver preparations were given intravenously. From their results the authors conclude that pernicious anemia and pellagra are due to different causes. They also suggest that normal livers contain a substance other than the erythrocyte-maturing factor which is absent in the livers of pellagrins.

Several years ago, Wilkinson and Israels described a disease (achrestic anemia) characterized by macrocytic anemia due to inability of the bone marrow to utilize the erythrocyte-maturing factor, the presence of free hydrochloric acid in the gastric contents and a fatal prognosis. Wauchope and Leslie-Smith⁷⁸ and Mahler and Greenberg⁷⁹ describe cases which they consider typical of this syndrome.

HEMOLYTIC ANEMIA

The hemolytic anemias comprise a group of blood dyscrasias which have multiple etiologic factors. It is necessary to recognize the causative agent for purposes of diagnosis, prognosis and treatment. The hemolytic anemias of childhood are characterized by reticulocytosis, leukocytosis, hyperplastic bone marrow and occasionally bony adsoption. Parsons⁸⁰ lists erythroblastosis foetalis, acute hemolytic anemia, reactive reticulocytosis, congenital hemolytic jaundice, sickle cell anemia and Cooley's anemia as members of this group. The similarity of icterus gravis, congenital anemia of the newborn and erythroblastosis is pointed out by Miller⁸¹ in a case study of a family in which all three diseases were present. Henderson⁸² has studied several cases of anemia of the newborn and of early infancy. He states that the anemia of prematurity is an exaggeration of physiologic hemolysis, that it is hyperchromic and that the cause is unknown. In most instances the prognosis is good.

Congenital hemolytic jaundice, although it may manifest itself in infancy, can occur at any age. Mandelbaum⁸³ reports a case in which an initial crisis occurred in a patient 75 years old who was cured by splenectomy. The usual characteristics of the malady were present—

78 Wauchope, G. M., and Leslie-Smith, M. Macrocytic Anaemia of the Achrestic Type, *Lancet* **2** 1518, 1938.

79 Mahler, A., and Greenberg, D. A Case of Hyperchromic Macrocytic Anemia Refractory to Liver Extract, *J. A. M. A.* **112** 1150 (March 25) 1939.

80 Parsons, L. G. The Haemolytic Anemias of Childhood, *Lancet* **2** 1395, 1938.

81 Miller, H. C. The Familial Occurrence of Icterus Gravis, Congenital Anemia of the Newborn and Erythroblastosis Fetalis. Case Study, *Yale J. Biol. & Med.* **11** 363, 1939.

82 Henderson, J. L. Anaemias of the Newborn and Early Infancy, *Tr. Edinburgh Obst. Soc.*, 1938-1939, p. 63, in *Edinburgh M. J.*, March 1939.

83 Mandelbaum, H. Congenital Hemolytic Jaundice. Report of a Case of Congenital Hemolytic Jaundice, Initial Hemolytic Crisis Occurring at the Age of Seventy-Five, Splenectomy Followed by Recovery, *Ann. Int. Med.* **13** 872, 1939.

jaundice, an enlarged spleen, small round cells (which were fragile) and reticulocytosis. The unusual occurrence of ulcer of the leg in a case of hemolytic jaundice is noted by Taylor⁸⁴. Such a lesion may be bilateral and usually occurs on the medial malleolus. Local therapy is of little value, but healing often results after splenectomy. Watson⁸⁵ reports a study of 35 patients with hemolytic jaundice. Twenty of these had microcytic anemia, increased fragility of the red blood cells and absence of autoagglutination. In the remaining 15, macrocytic anemia predominated, there was little, if any, evidence of increased fragility of the red blood cells, and autoagglutination occurred in 2 instances. The author calls attention to the fact that there was no parallelism between the anemia and the jaundice. This suggested sluggish excretion of bilirubin by the liver, which was considered beneficial rather than detrimental to the patient.

As an accurate method of determining the increased fragility of the red blood cells in cases of hemolytic jaundice, Guest and Wing⁸⁶ used the Van Allen hematocrit tubes. Measured amounts of red blood cells were drawn into standardized tubes and diluted with saline solution of varying concentrations. Changes in volume as well as beginning and complete hemolysis were noted.

One of the more serious complications often observed in association with the administration of sulfanilamide and sulfapyridine is hemolytic anemia. Koletsky⁸⁷ states that the anemia is not related to the type of infection, the dose of the drug or the concentration of the drug in the serum. He reported 2 deaths due to hemolytic anemia following treatment with sulfanilamide. Garvin⁸⁸ describes two types of hemolytic anemia—acute and chronic. The latter is mild, develops slowly and is not associated with jaundice, but there is excessive excretion of urobilinogen. The acute type has an abrupt onset in two to three days. Withdrawal of the drug and transfusions were beneficial to the patients. Antopol and his colleagues⁸⁹ note the occurrence of acute hemolytic

84 Taylor, E. S. Chronic Ulcer of the Leg Associated with Congenital Hemolytic Jaundice, *J. A. M. A.* **112** 1574 (April 22) 1939.

85 Watson, C. J. Hemolytic Jaundice and Macrocytic Hemolytic Anemia. Certain Observations in a Series of Thirty-Five Cases, *Ann. Int. Med.* **12** 782, 1939.

86 Guest, G. M., and Wing, M. A Method for the Determination of Erythrocyte Fragility, Using Van Allen Hematocrit Tubes for the Measurement of Changes in Volume of the Cells in Hypotonic Salt Solutions, *J. Lab. & Clin. Med.* **24** 850, 1939.

87 Koletsky, S. Fatal Hemolytic Anemia Following the Administration of Sulfanilamide, *J. A. M. A.* **113** 291 (July 22) 1939.

88 Garvin, C. F. Complications Following the Administration of Sulfanilamide, *J. A. M. A.* **113** 288 (July 22) 1939.

89 Antopol, W., Applebaum, I., and Goldman, L. Two Cases of Acute Hemolytic Anemia with Auto-Agglutination Following Sulphanilamide Therapy, *J. A. M. A.* **113** 488 (Aug. 5) 1939.

anemia associated with autoagglutination following sulfanilamide therapy Plummer and Ensworth⁹⁰ reported the presence of severe anemia in 270 patients with pneumonia treated with sulfapyridine They also called attention to the fact that several of these patients had mild anemia Similar results from the use of drugs of the sulfanilamide group are noted by Morgan and Detweiler,⁹¹ Price and Myers⁹² and MacLeod⁹³ It is suggested by MacLeod that toxic effects from these drugs are more common than is expected and that more than routine studies should be employed to detect them

Hemolytic anemia was produced in dogs and monkeys after administration of sulfanilamide by P'An⁹⁴ Machella and Higgins⁹⁵ observed anemia in rats following the use of sulfanilamide They conclude that the severity of the anemia varies with the dose of the drug and that recovery follows withdrawal of the drug On the basis of the minimal concentration in the blood necessary to produce anemia, Richardson⁹⁶ compared the toxicity of sulfanilamide, sulfapyridine and diaminodiphenylsulfone Sulfapyridine was the least toxic and diaminodiphenylsulfone the most toxic

Erf and MacLeod⁹⁷ determined quantitatively the amount of urobilin excreted by 20 patients with pneumonia treated with sulfapyridine and employed this method as an index of hemolysis The amount of urobilin excreted varied with the anemia, and both were directly proportional to the dose of the drug All evidence of destruction of red blood cells disappeared when the sulfapyridine was withdrawn

The effect of various hemolytic agents on red blood cells has been investigated by Dameshek, Schwartz and Singer⁹⁸ They employed

90 Plummer, N, and Ensworth, H J Sulfapyridine in the Treatment of Pneumonia, *J A M A* **113** 1847 (Nov 18) 1939

91 Morgan, J R E, and Detweiler, H K The Hematologic Study of Seventy-Six Pneumonia Cases Treated with Sulfapyridine, Including a Fatal Case of Agranulocytosis, *J Lab & Clin Med* **25** 275, 1939

92 Price, A E, and Myers, G B Treatment of Pneumococcic Pneumonia with Sulfanilamide, *J A M A* **112** 1021 (March 18) 1939

93 MacLeod, C A Chemotherapy of Pneumococcic Pneumonia, *J A M A* **113** 1405 (Oct 7) 1939

94 P'An, S Y Observations on the Chronic Effect of Sulfanilamide in Dogs and Monkeys with Particular Reference to the Blood, *Chinese M J* **56** 111, 1939

95 Machella, T E, and Higgins, G M Anemia Induced in Rats by the Administration of Sulfanilamide, *Proc Staff Meet, Mayo Clin* **14** 183, 1939, Anemia Induced in Rats by Means of Sulphanilamide, *Am J M Sc* **198** 804, 1939

96 Richardson, A P The Production of Anemia in White Mice by Sulfanilamide, Sulfapyridine and Diaminodiphenylsulfone, *J Pharmacol & Exper Therap* **67** 429, 1939

97 Erf, L A, and MacLeod, C M Hemolysis from Sulfapyridine, *J Clin Investigation* **18** 472, 1939

98 Dameshek, W, Schwartz, S O, and Singer, K Spherocytosis (and Increased Erythrocyte Fragility) as Indicators of Hemolytic Activity, with a Consideration of "Differential" Fragility, *J Clin Investigation* **18** 479, 1939

this method in an attempt to distinguish the various types of hemolytic anemias. It was noted that distilled water, saponin, phenylhydrazine, lysolecithin and immune hemolytic serum would produce spherocytosis of varying degree, depending on the dose. The changes observed in the bone marrow and in the peripheral blood indicate that spherocytosis developed outside the bone marrow. It was also noted that all the spherocytes reacted in the same manner to varying dilutions of saline solution but differed in their reactions to the hemolysins. This physiologic difference is considered important in distinguishing the various hemolytic anemias.

Cases of Lederer's anemia with the characteristic blood picture are reported by Drummond,⁹⁹ Levy and Miller¹⁰⁰ and Boquien¹⁰¹. All of these investigators discuss the various possible etiologic factors and conclude that the cause is not known. They also state that transfusions are specific. McGavack¹⁰² reports a similar case of acute hemolytic anemia in a 17 year old girl, but as transfusions did not aid the patient he feels that this was not a case of Lederer's anemia. Hamilton¹⁰³ describes a syndrome characterized by chills, fever, dark urine, oliguria and splenomegaly, occurring in a 2 year old boy. The patient had several remissions and relapses. The author expresses the opinion that this case simulated Lederer's anemia but believes that the condition is a distinct clinical entity and that it should be named "acute hemocytolytic anemia."

SICKLE CELL ANEMIA

Diggs and Bibb,¹⁰⁴ of Memphis, Tenn., present an excellent study of the status of the erythrocyte in 47 patients with active sickle cell anemia. They observed that in sealed cover slip preparations there occurs an increase in the carbon dioxide content of the serum in which the erythrocytes are suspended within a few hours. Coincidentally with this, the red blood cells assume many bizarre forms. The change is from the normal round shape with even distribution of hemoglobin to a many-pointed form, thick in one portion and thin in another. Elliptic, oat-shaped or crescent-shaped erythrocytes, which are present when the blood is drawn, have apparently passed through the process just

99 Drummond, J. A Case of Lederer's Anaemia, *South African M. J.* **13** 406, 1939.

100 Levy, W., and Miller, W. J. Acute Hemolytic Anemia Lederer Type, *Am. J. Dis. Child.* **58** 349 (Aug.) 1939.

101 Boquien, Y. Trois cas -dont deux familiaux- d'anémie hémolytique aigue (maladie de Lederer-Brill), *Sang.* **13** 320, 1939.

102 McGavack, T. H. Acute Hemolytic (Lederer's) Anemia, *New England J. Med.* **220** 140, 1939.

103 Hamilton, D. G. A Case of Acute Haemocytolytic Anaemia with Haemoglobinuria, *M. J. Australia* **1** 305, 1939.

104 Diggs, L. W., and Bibb, J. The Erythrocyte in Sickle Cell Anemia, *J. A. M. A.* **112** 695 (Feb. 25) 1939.

described and do not undergo further significant change. When the blood in sealed moist preparations is exposed to the air, the bizarrely shaped cells, which are in the initial stages of sickling, revert to the round forms, and the true sickle cells become less pointed but do not become round.

According to these observers, the typical characteristic sickle cell averages 10 to 20 microns in length and 2 to 4 microns in width. It is hyperchromic, elongated, pointed at each end and curved in the middle. Rarely is it observed in any other condition than true sickle cell anemia. The percentage of these abnormally shaped cells in stained films made in the usual manner varies from none to over 50 per cent, apparently there is no relation between the number of sickle cells and the severity of the anemia.

Measurements of the red blood cells of patients in whom less than 5 per cent of the cells were elongated showed marked anisocytosis and mean diameters which were greater than normal, averaging between 7.8 and 9.5 microns. The average mean corpuscular volume was 90 cubic microns, the average mean corpuscular hemoglobin was 29 micro-micrograms, and the average mean corpuscular hemoglobin concentration was 32 per cent. These figures indicate that the erythrocytes in cases of sickle cell anemia are usually of the normocytic, normochromic type, with a tendency toward macrocytosis. The reticulocytes of the circulating blood are usually increased in the presence of active sickle cell anemia, in this series the average was 15 per cent.

The erythrocytes of patients with sickle cell anemia are more resistant than are normal cells to hypotonic saline solutions, and some of the cells even retain their hemoglobin in distilled water. In this study, hemolysis began in hypotonic salt solutions at an average of 0.34 per cent and was complete at 0.11 per cent, whereas the average figures for the control groups were 0.42 per cent and 0.32 per cent respectively. The resistance of erythrocytes of patients with the sickle cell trait in the absence of anemia was also slightly increased, as hemolysis began at 0.35 per cent and was complete at 0.2 per cent. Corresponding figures for the control group were 0.39 per cent and 0.27 per cent.

Mechanical shaking of oxalated or defibrinated blood at the rate of two hundred and fifty vibrations per minute did not cause a significant alteration in the red blood cell count or the cell volume in blood from normal persons or from patients with sickle cell anemia. When glass beads were added, however, and the carbon dioxide concentration in the air above the blood was increased, the red blood cells of patients with sickle cell anemia were destroyed more rapidly than were those of normal blood. It is concluded from these experiments that the carbon dioxide causes the red blood cells to become larger and the round cells in the blood of patients with sickle cell anemia to become sickled.

The sedimentation rate for patients with sickle cell anemia may be normal despite the presence of marked anemia. These observers interpret an increased sedimentation rate in the presence of this disease as indicative of some complication, such as active tuberculosis, salpingitis or badly infected ulcers of the leg.

Bunting¹⁰⁵ observed that sickled erythrocytes from patients with sickle cell anemia and the sickle cell trait did not form rouleaux and remained unsedimented after one hour of observation. Specimens of blood for this study were obtained from patients with sickle cell anemia and the sickle cell trait, and the percentage of sickle cells was increased to approximately 50 per cent by exposure to carbon dioxide. Specimens of the same blood which were not exposed to carbon dioxide and contained relatively few sickle cells formed rouleaux and sedimented at a rate of 23 to 70 mm in one hour. These studies would suggest that the delay in settling of the red blood cells is proportional to the percentage of sickle cells present.

Arena¹⁰⁶ reports the case histories of 5 Negro children with sickle cell anemia, in whom the first manifestation of the disease was the appearance of signs and symptoms indicative of cerebral vascular disease. All had right hemiplegia. Reference is made to a relatively small number of similar cases in the literature. It is emphasized that thrombotic phenomena are important episodes in the life history of patients with this type of anemia and that obliterative vascular changes and thrombi are part of the pathologic picture. It is the belief of some that the tendency to capillary engorgement and arterial thrombosis may be due to the abnormal shape of the red blood cells, which prevents their ready passage through the capillaries, and the tendency of these cells to agglutinate. Infection with fever, which causes increased sickling, may be a factor in causation of the thrombosis. In 1 patient necropsy showed a tendency to occlusion of the large subarachnoid arteries, which is similar to the changes observed in the splenic vessels. The author concludes that splenectomy should be given a further trial for patients with splenomegaly who have constitutional symptoms and previously have had a vascular accident.

Josey¹⁰⁷ reports the case of a Negro boy aged 8 years with sickle cell anemia, who at the age of 4 years had attacks persisting for a week or more in which he had difficulty in speaking, swallowing and walking. Two years later left hemiplegia appeared, which persisted for six weeks.

105 Bunting, H. Sedimentation Rates of Sickled and Non-Sickled Cells from Patients, *Am J M Sc* **198** 191, 1939.

106 Arena, J. M. Sickle Cell Anemia, Cerebral Vascular Lesions Accompanying Anemia, *J Pediat* **14** 745, 1939.

107 Josey, A. I. Sickle Cell Anemia with Cerebral Thrombosis (Case), *South M J* **32** 915, 1939.

A year later, at the age of 7 years, the hemiplegia again occurred, and this time it was associated with aphasia. Fifteen weeks later the weakness on the left side was improved somewhat, and speech had partially returned. One year after this there was slight improvement in the patient's neurologic condition, but the general picture remained the same. This case is reported as probably representing recurrent cerebral thrombosis associated with sickle cell anemia.

Bridges¹⁰⁸ reviews the literature dealing with cerebral vascular accidents in patients with sickle cell anemia and states that in none of the cases thus far reported has a satisfactory account of the origin and nature of the cerebral clinical disturbances been offered. Two cases of sickle cell anemia with cerebral vascular manifestations are reported, with a discussion of the pathogenesis of the lesions of the central nervous system and a consideration of the general problem of the disease. It is suggested that the obliterative vascular changes in the spleen previously described by Diggs may occur likewise in the cerebral vessels from the same cause. From the studies reported by Bridges it is concluded that the clinical evidences of cerebral lesions may arise from two different pathologic changes. The large subarachnoid cerebral arteries may undergo gradual obliteration with final complete closure as a result of endarterial intimal proliferation and not of thrombosis. This process is identical with that which causes occlusion of the splenic arteries. A second obscure process also occurs, which is quite different from endarterial intimal proliferation. This change is in connection with the small intracerebral vessels and is responsible for multiple focal necroses and hemorrhages in the brain.

Page and Silton¹⁰⁹ report the effect of pregnancy in 2 cases of acute sickle cell anemia. One patient, aged 19, in whose case there were a red blood cell count of 1,660,000 per cubic millimeter and a hemoglobin concentration of 42 per cent, was first observed three weeks from term, liver extract, copper and iron were given orally. The patient had a normal spontaneous delivery, and seven months later the mother had no complaints referable to the anemia, although the red blood cell count was approximately 2,000,000 per cubic millimeter. The baby, whose blood did not show sickling, was in good condition at the age of 7 months. The second patient, aged 20 years, was five months pregnant when first seen, the red blood cell count was 1,920,000 per cubic millimeter and the concentration of hemoglobin was 35 per cent. She was acutely ill, and a clinical diagnosis of bilateral bronchopneumonia was made. Death occurred twenty-two hours after admission, and

108 Bridges, W. H. Cerebral Vascular Disease Accompanying Anemia, *Am J Path* **15** 353, 1939.

109 Page, E. W., and Silton, M. Z. Pregnancy Complicated by Sickle-Cell Anemia, *Am J Obst & Gynec* **37** 53, 1939.

necropsy showed sickle cell anemia, thrombophlebitis of the pelvic veins, embolism of the pulmonary arteries with multiple infarcts, twin pregnancy (5 months) and severe siderofibrosis of the spleen. The authors conclude that pregnancy may be a factor in producing an exacerbation of the disease but that patients may be carried successfully to term when proper measures are employed.

ERYTHROBLASTIC AND LEUKOERYTHROBLASTIC ANEMIAS

Several examples of leukoerythroblastic anemia in adults have been described. Vaughan defined this condition as "an anemia characterized by the presence, in the peripheral blood, of immature red blood cells and a few immature white blood cells of the myeloid series." In 2 cases described by Vaughan and Harrison¹¹⁰ there were splenomegaly, irregular density of the spongiosa of long bones and throughout the flat bones associated with decreased density of the cortex of the long bones, the inner edge of the cortex being frayed and irregular in appearance (myelosclerosis), leukoerythroblastic anemia and increased fragility of the red blood cells in hypotonic saline solutions, associated with increased thickness of the cells. The condition was confused at different stages of its evolution with polycythemia and leukemia. Cases have been described under the names erythroleukemia, atypical myeloid leukemia, aleukemic myelosis, myelophthisic splenomegaly, myelosclerosis, myelosis with osteosclerosis and myelosclerosis associated with a leukemoid blood picture.

Of the 3 cases described by Gear and Becker,¹¹¹ the condition in 2 was associated with carcinomatosis, and in 1, with multiple myelomatosis. The disease is grouped with Cooley's erythroblastic anemia, but the pathogenesis is essentially different.

Diamond¹¹² presents an excellent review of the general subject of erythroblastic anemias in infancy and childhood. In the first group is erythroblastemia secondary to some obvious underlying cause (excessive exposure to roentgen rays or to radioactive material, chemical and drug poisoning, generalized malignant disease with metastasis to the bone marrow, steatorrhea, recurrent and severe hemorrhage, chronic or severe infection, congenital syphilis, congenital malformations of the circulatory system or hemolytic anemia), while in the second group are anemias of unknown origin (Mediterranean anemia and the anemia of

110 Vaughan, J. M., and Harrison, C. V. Leuco-Erythroblastic Anaemia and Myelosclerosis, *J. Path. & Bact.* **48** 339, 1939.

111 Gear, J., and Becker, L. H. Leuco-Erythroblastic Anaemia. Report of Three Cases, *South African M. J.* **13** 13, 1939.

112 Diamond, L. K. The Erythroblastic Anemias, in *A Symposium on the Blood and Blood-Forming Organs*, Madison, Wis., University of Wisconsin Press, 1939, p. 57.

erythroblastosis foetalis) The treatment of Mediterranean anemia and of erythroblastosis foetalis is symptomatic and nonspecific, and the results are unsatisfactory

Nittis¹¹³ explains the peculiar structure of the diploe in cases of erythroblastic anemia by outward expansion of the marrow as a result of continuously stimulated hemopoiesis The trabeculae connecting the two plates become elongated, producing a bristle-like appearance on the roentgen plate

In a detailed description of 5 typical cases of Cooley's anemia, Francaviglia¹¹⁴ notes that there was increased resistance of the red blood cells in the parent who transmitted the disease and in the apparently normal brothers and sisters of the patients For patients with atypical forms of the disease with slow evolution, thyroid, liver extract and iron were of therapeutic value in prolonging life

The essential pathologic features, as noted by Schiappoli¹¹⁵ in 2 cases, are a process of general reabsorption of the bones with formation of new trabeculae, diffuse hyperplasia of the reticuloendothelial system, hemolytic anemia and increased medullary and extramedullary hemopoiesis Constitution and familial predisposition are considered important factors in the disease, but the cause is unknown

In cases of erythroblastic anemia with jaundice in children and adolescents, Acuña and Bonduel¹¹⁶ found that damage to the liver was caused by the products of hemolysis The peripheral blood in this condition is characterized by large numbers of immature red blood cells and leukocytes The hepatomegaly and other features at times suggest von Jaksch's pseudoleukemia The behavior of the pigments and their decomposition products is different from that observed with congenital splenomegalic hemolytic jaundice, suggesting that these are two different clinical forms of congenital hemolytic jaundice

Andrus and Holman¹¹⁷ removed the spleen from 4 children with Cooley's erythroblastic anemia One died in five months, a second in two years Two, alive three and one-half years and four years respectively after operation, were in fair condition, but the anemia persisted

113 Nittis, S The Mechanism of the Production of Bone Changes in the Plastic Anemias, *Univ Hosp Bull*, Ann Arbor **5** 27, 1939

114 Francaviglia, A Ricerche sul morbo di Cooley, studio clinico su alcuni casi di morbo di Cooley osservati in Puglia, *Arch per le sc med* **68** 395, 1939

115 Schiappoli, F Ricerche sul morbo di Cooley, il reperto anatomico, *Arch per le sc med* **68** 457, 1939

116 Acuña, M, and Bonduel, A A Alteraciones hepáticas en el curso de las anemias eritroblásticas Ictericias eritroblásticas, *Prensa med argent* **25** 2444, 1938

117 Andrus, W DeW, and Holman, C W Splenectomy in Various Blood Disorders, *Ann Surg* **109** 64, 1939

In a case reported by Macklin, Lamont and Macklin,¹¹⁸ erythroblastosis foetalis accompanied by hemolysis was present in a newborn girl. Of the other pregnancies of the mother, 5 of 7 ended in miscarriages or premature delivery, suggesting a possibility of a similar blood dyscrasia which prevented development of the fetus. The authors feel that the disease represents derangement of blood formation in the fetus rather than persistence of a normal fetal blood picture.

Thalheimer, Mezzetti and Gershon-Cohen¹¹⁹ described a case of Cooley's Mediterranean anemia in a 14 year old Italian girl, this makes the seventh case of this type in the literature. The illness dated from the first year of life. Physical examination showed mongoloid facies, a large heart, a protruding abdomen, hepatomegaly and characteristic roentgen changes in bone. The spleen had been removed at the age of 5 years. The blood was characterized by hypochromic anemia and leukocytosis.

Moore and Pastore¹²⁰ noted erythroblastic splenomegaly in a pregnant Negress. Erythroblastic foci were found in the spleen, liver and lymph nodes, but the bone marrow was not grossly abnormal. It is thought that infection (pneumonia, tuberculosis, renal abscesses and rheumatic fever) combined with pregnancy induced the alterations in the hemopoietic tissue. There were some appearances in the internal organs resembling leukemia, and 10 per cent myeloblasts were observed in the peripheral blood.

Erythroblastic anemia in 2 brothers aged respectively 17 and 20 years is described by Atkinson.¹²¹ There was no evidence of a hereditary origin of the disease, although the red blood cells of the father, the mother and one of 2 sisters showed greater resistance in diluted saline solution than did those of normal controls (hemolysis complete, 0.08 per cent, 0.04 per cent, 0.08 per cent, controls, 0.22 per cent to 0.28 per cent).

A case of acute erythromyelosis in a 25 year old woman is described by Chevallier and Ely.¹²² Anemia, leukopenia, fever and a hemorrhagic tendency characterized the disease. On sternal puncture 82 per cent of the cells were observed to be erythroblasts, and in the peripheral blood nucleated red blood cells numbered 51,920 per cubic millimeter.

118 Macklin, M. T., Lamont, J. A., and Macklin, C. C. Erythroblastosis Foetalis. Report of a Case, *Am J Dis Child* **57** 349 (Feb.) 1939.

119 Thalheimer, E. J., Mezzetti, A., and Gershon-Cohen, J. Cooley's Anemia (Mediterranean Anemia), with Report of a Case in an Adolescent, *J. Pediat.* **14**, 349, 1939.

120 Moore, R. A., and Pastore, J. B. Note on Erythroblastic Splenomegaly Occurring During Pregnancy, *Am J M Sc* **198** 187, 1939.

121 Atkinson, D. W. Erythroblastic Anemia. Report of Two Cases in Adult Siblings, with a Review of the Theories as to Its Transmission, *Am J M Sc* **198** 376, 1939.

122 Chevallier, P., and Ely, Z. Erythromyelose aigue, *Sang* **13** 106, 1939.

APLASTIC ANEMIA

Rhoads,¹²³ summarizing an extensive study of aplastic anemia, divides refractory anemia into five histologic types that with hypocellular bone marrow, that with immature cellular marrow, that with active cellular marrow, that with sclerosis of the marrow and that with megakaryocytic marrow. The disease may have definite but temporary remissions, in some cases induced by splenectomy. In 6 cases definite exacerbations followed exposure to sunlight. Toxemia may play a part in the production of the disease, the several types having varying responses to cyclic chemical compounds of endogenous or exogenous origin.

Huber¹²⁴ studied the blood and bone marrow of relatives of 4 patients who died of panmyelophthisis. A common finding was neutropenia or lymphocytosis, suggesting a familial diathesis to disease of the bone marrow with congenital or inherited weakness of the marrow. The pathologic feature was imbalance of the neutrophil-leukocyte content of the blood.

Longworth, Shedlovsky and MacInnes¹²⁵ found that the gamma globulin-albumin ratio in the serum of patients with aplastic anemia is above normal.

Rein and Wise¹²⁶ reported a case of aplastic anemia in a 30 year old woman after mapharsen treatment, with a fatal termination. There were multiple petechial and ecchymotic hemorrhages of the arachnoid, visceral pleura, epicardium, endocardium, renal capsules, ileum and cecum, with toxic hepatitis and hyperplastic splenitis.

A case of aplastic anemia following intravenous injection of a gold compound is reported by Wintrobe, Stowell and Roll.¹²⁷ Recovery followed nine blood transfusions and hysterectomy. These authors did not succeed in producing aplastic anemia by intravenous injection of a gold compound into rabbits. In cases collected from the literature, 6 patients with idiopathic aplastic anemia and 13 of a group with post-arsenical aplastic anemia survived one year or longer.

123 Rhoads, C. P. Aplastic Anemia, in *A Symposium on the Blood and Blood-Forming Organs*, Madison, Wis., University of Wisconsin Press, 1939, p. 31.

124 Huber, H. Stammbaumuntersuchungen bei Panmyelophthisekranken, *Klin Wchnschr.* **18** 1145, 1939.

125 Longworth, L. G., Shedlovsky, T., and MacInnes, D. A. Electrophoretic Patterns of Normal and Pathological Human Blood Serum and Plasma, *J. Exper. Med.* **70** 399, 1939.

126 Rein, C. R., and Wise, F. Mapharsen in Treatment of Syphilis in Office Practice. A Study Based on 2,342 Injections in One Hundred and Thirteen Patients, *J. A. M. A.* **113** 1946 (Nov. 25) 1939.

127 Wintrobe, M. M., Stowell, A., and Roll, R. M. Report of a Case of Aplastic Anemia Following Gold Injections in Which Recovery Occurred, *Am. J. M. Sc.* **197** 698, 1939.

In cases of aplastic anemia Jordan¹²⁸ finds that the lymphoid structure of the lymph nodes, the spleen and the marrow is identical. The predominant cell in the three tissues is the lymphocyte, which Jordan considers an immature polyvalent cell. The small lymphocytes grow to become large lymphocytes, which differentiate into erythrocytes in the venous sinuses and into granulocytes in the intervascular stroma.

Ingraham¹²⁹ reports a case of aplastic anemia with fatal termination, following the use of triarsen and bismuth salicylate during pregnancy. The red blood cell count before transfusion fell to 780,000 per cubic millimeter, and the terminal leukocyte count was 1,800 per cubic millimeter, with 5 per cent neutrophils.

In Boon's¹³⁰ case aplastic anemia followed arsphenamine therapy. Twenty-five transfusions totaling 12,540 cc of blood were given, without evidence of spontaneous regeneration of blood. After the transfusions were discontinued there was a rise in the number of reticulocytes and of red blood cells, followed by recovery. The granulocytes recovered more slowly than did the red blood cells.

In the treatment of a moribund patient with aplastic anemia, Osgood, Riddle and Mathews¹³¹ tried intravenous injection of bone marrow suspended in the donor's blood. The cells disappeared rapidly from the circulation. There was no untoward reaction, but the authors express doubt that there was any therapeutic benefit from the procedure. During fifty-two days, forty-three blood transfusions were given, totaling 21,870 cc. Death was due to sepsis with terminal bronchopneumonia. Pentose nucleotide and liver extract were ineffective.

HEMATOLOGIC CHANGES ASSOCIATED WITH INFECTION

Leukemoid reactions of the myeloid type have been classified recently by Heck and Hall¹³². These authors stress the fact that the hematologic picture simulates that of leukemia, but at autopsy there is no evidence to support this diagnosis. In the presence of pyogenic infections there are an increase in the polymorphonuclear neutrophils, increasing numbers of immature cells and degenerative changes of the leukocytes. The degree of alterations is dependent on the virulence of the organism. The

128 Jordan, H. E. Aplastic Anemia, with Special Reference to the Significance of the Small Lymphocytes, *Arch. Path.* **27**: 1 (Jan.) 1939.

129 Ingraham, N. R. Complications Due to Arsenical Therapy in Syphilitic Pregnant Women, *J. A. M. A.* **112**: 1537 (April 22) 1939.

130 Boon, T. H. Aplastic Anemia with Complete Recovery, *Brit. M. J.* **2**: 1041, 1938.

131 Osgood, E. E., Riddle, M. C., and Mathews, T. J. Aplastic Anemia Treated with Daily Transfusions and Intravenous Marrow. Case Report, *Ann. Int. Med.* **13**: 357-367 (Aug.) 1939.

132 Heck, F. J., and Hall, B. E. Leukemoid Reactions of the Myeloid Type, *J. A. M. A.* **112**: 95 (Jan. 14) 1939.

resistance of the host, the site and extent of the infection and the reactivity of the bone marrow. These changes in the blood are seen most often in children. Diseases which may produce a similar hemopoietic response are specific blood dyscrasias, such as pernicious anemia, hemolytic anemia and polycythemia, hyperplasia of the bone marrow associated with acute hemorrhage or with any severe anemia, and, lastly, diseases involving the bone and bone marrow. Heck and Hall state that since there are a resemblance in the blood picture to that of leukemia and a leukemoid response, it is necessary to differentiate the conditions for purposes of treatment and prognosis.

Amidon¹³³ made careful hematologic studies in cases of acute infections. White blood cell counts, differential counts, filament-nonfilament counts and estimation of the toxic granulation of the polymorphonuclear neutrophils and of the vacuolization of the cytoplasm were done in 330 cases. After establishing his own criteria for mild, moderate, severe and grave infections, the author endeavors to evaluate the changes which occur with infection. He notes that in a series of 14 cases of appendicitis the filament-nonfilament index was altered in every instance, toxic granulation was observed in 73 per cent of the cases studied, and degenerative changes in the leukocytes were recorded in 43 per cent. Similar observations were made in cases of pneumonia and in a series of cases of miscellaneous infections.

In 39 cases of bacillary dysentery Ginsburg and his co-workers¹³⁴ observed a normal white cell count or mild leukocytosis. A "shift to the left" of the neutrophils was noted in 95 per cent of the cases. With recovery the hematologic picture reverted to normal. Gezelius¹³⁵ studied the changes in the blood in 31 cases of rheumatic fever. It is his opinion that the occurrence and severity of the anemia are an accurate index of the activity of the disease. He also points out that the sedimentation rate parallels the severity of the anemia and that both the anemia and the sedimentation rate should be carefully followed to determine the course of the disease. It is also the opinion of Hubbard and McKee¹³⁶ that anemia is an indication of acute rheumatic fever.

Schmid¹³⁷ investigated the blood and bone marrow in cases of undulant fever. His observations led him to conclude that the changes

133 Amidon, E. L. Hematologic Studies in Acute Infections, *J. Lab. & Clin. Med.* **24** 1009, 1939.

134 Ginsburg, H. M., Hirschberg, E. M., and Brisker, F. Bacillary Dysentery, *J. A. M. A.* **113** 1321 (Sept. 30) 1939.

135 Gezelius, G. Die Anämie bei akuten rheumatischem Fieber im Kindesalter, *Acta pædiat.* **23** 361, 1939.

136 Hubbard, J. P., and McKee, M. H. The Anemia of Rheumatic Fever, *J. Pediat.* **14** 66, 1939.

137 Schmid, N. Blut und Knochenmark bei Morbus Bang, *Schweiz. med. Wchnschr.* **69** 191, 1939.

associated with undulant fever are similar to those observed in cases of typhoid fever. There is occasionally mild anemia. The white cells are usually reduced but occasionally normal in number. Lymphocytosis predominates, and often there is monocytosis. Associated with the neutropenia is a "shift to the left" of the polymorphonuclear neutrophils. The eosinophils are absent, and the platelets are unaltered. Studies of the blood in about 300 cases of brucellosis were also made by Calder and his associates¹³⁸. Their results are similar to those of Schmid. These authors emphasize that this blood pattern is specific for Bang's disease.

The opinion of Vaizey and Clark-Kennedy¹³⁹ in regard to the anemia occurring with infections is most interesting. These authors point out that the early literature stated that dental sepsis is often considered the cause of anemia but that in the light of recent investigations there is little proof or evidence to support this view. Hemoglobin metabolism in the presence of chronic infection was studied by Vaughan and Saifi¹⁴⁰. They noted a hyperplastic and not an aplastic marrow in association with the usual normocytic orthochromic anemia. Their studies on urobilinogen excretion gave no supportive evidence of an abnormal breakdown of hemoglobin. Porphyrin excretion was increased, and to the authors this suggested a disturbance in hemoglobin synthesis or degradation. In conclusion the authors state that this abnormality of hemoglobin synthesis is dependent on the presence of infection and is responsible for the anemia associated with a chronic septic process.

ANEMIA ASSOCIATED WITH CANCER

Although anemia has been identified for many years as a clinical aid in the diagnosis of cancer, the method of its production is not definitely known. The type of cancer, its site, the presence or absence of metastasis, the occurrence of bleeding and the questionable effect of a toxic cancerous agent on the bone marrow must all be included in considering the pathogenesis of the anemia. Various types of anemia have been described.

Monasterio¹⁴¹ studied the morphologic and pathologic aspects of hemopoiesis in 33 cases of carcinoma of the stomach. Normocytic hypochromic anemia was the most common, less frequently normochromic anemia was observed, and rarely was hyperchromic anemia noted. The

138 Calder, R. M., Steen, C., and Baker, L. Blood Studies in Brucellosis, *J. A. M. A.* **112** 1893 (May 13) 1939.

139 Vaizey, J. M., and Clark-Kennedy, A. E. Dental Sepsis in Relation to Anaemia, Dyspepsia, and Rheumatism *Brit. M. J.* **1** 1269, 1939.

140 Vaughan, J. M., and Saifi, M. F. Haemoglobin Metabolism in Chronic Infection, *J. Path. & Bact.* **49** 69, 1939.

141 Monasterio, G. La sindrome anemica del carcinoma gastrico e sua patogenesi, *Haematologica* **20** 443, 1939.

bone marrow was normal in most instances but was occasionally hyperplastic. The author states that in some atypical cases megaloblasts and basophilic normoblasts were predominant in the bone marrow. He also describes the rare occurrence of plasma cells and histiocytes.

It is suggested by Liechti¹⁴² that such secondary diseases as gastric cancer and tuberculosis, when present in a patient with known pernicious anemia, do not exaggerate the macrocytic anemia but rather alter the blood picture and produce microcytic anemia. This author points out that, since the hemopoietic changes often precede the clinical symptoms, patients with pernicious anemia should be carefully studied not only as regards relapse but for the occurrence of complications.

The pathogenesis of the anemia associated with gastric carcinoma was investigated by Schenken and his associates.⁵ At autopsy the stomach showed a widespread neoplasm involving the entire prepyloric and pyloric areas, the entire mucosa was replaced by malignant tissue. There was no evidence of metastasis. An extract was prepared from the liver of the patient and given to a patient with pernicious anemia in relapse. No response was observed, although the patient subsequently responded to a similar extract prepared from the liver of a patient who died as a result of a cerebral hemorrhage. Apparently the patient with the gastric carcinoma was unable to produce any intrinsic factor, and consequently the liver was deprived of its reserve of erythropoietic maturing substance. This observation is certainly in agreement with the present conception of the physiology of hemopoiesis.

ANEMIA ASSOCIATED WITH ENDOCRINE DYSFUNCTION

A clinical investigation of the relation of the hemopoietic phenomena to endocrine disorders in women was made by Sharp and Mack.¹⁴³ Approximately 25 per cent of the 450 patients studied had anemia. In the group that had primary pituitary-thyroid disorders, including patients from the menarche to the age of 24, the blood usually showed normocytic anemia, and hypochromic anemia, was rare. Purpura was common and was often accompanied with a prolonged bleeding time. The platelets were normal or decreased in number. Women ranging in age from 25 to 39 were included in the group with "secondary thyro-ovarian failure." Hypochromic microcytic anemia was usually present. Thrombopenia and purpura were observed frequently. Other important characteristics were koilonychia, achlorhydria, dry skin, brittle hair, pallor, dysphagia and glossitis. In the last group, which included

142 Liechti, H. *Zweite Krankheit bei pernicioser Anämie*, Schweiz med Wchnschr **69** 172, 1939.

143 Sharp, E. A., and Mack, H. C. *The Relationship of Hemopoietic Phenomena to Endocrine Disorders in Women*, Endocrinology **24** 202, 1939.

women from the age of 39 to the menopause, hypochromic microcytic anemia was predominant

In summary, these authors point out that in 35.2 per cent of the 68 cases of anemia reported the condition occurred in women in the first group. They suggest that combined therapy be given for the glandular dyscrasia and the anemia as needed. In their opinion, since normocytic normochromic anemia occurs in younger persons and microcytic hypochromic anemia in the older age groups, the latter type of anemia is an evidence of chronicity.

The production of anemia by injections of pituitrin (solution of posterior pituitary extract) was reported by Dodds and Noble and reviewed in one of our previous articles. These investigators believe that the extract has a specific effect on the red blood cells. Gilman and Goodman¹⁴⁴ have verified the "pituitary anemia" but emphasize the fact that the substance injected alters the electrolytes in the plasma, with a subsequent change in the osmotic pressure and rupturing of the red blood cells. Dohan, Jeffers and Creskoff¹⁴⁵ have also noted anemia following the injection of extract of anterior pituitary in dogs. These authors, however, made no effort to explain the pathogenesis of the anemia.

The sternal marrow of normal persons and that of patients with hyperthyroidism and hypothyroidism were studied by Jones¹⁴⁶. In the normal marrow approximately 6.2 per cent of the cells were nucleated, and the myeloid-erythroid ratio was 2.1 to 4.1. In the marrow from persons with hyperthyroidism there were 13.5 per cent of nucleated cells, and the myeloid-erythroid ratio was 5.1 to 20.1. Bone marrow from patients with myxedema revealed some atrophy. There were approximately 2.4 per cent of nucleated cells, and the myeloid-erythroid ratio was 1.1 to 3.1. Anemia was present in the 7 cases of myxedema investigated, there was no alteration in the blood of the 12 patients with hyperthyroidism. Microcytic, macrocytic and normocytic anemias occurred in the myxedematous group. The last-mentioned type was the most common. With adequate treatment the bone marrow returned to normal, and the anemia was eliminated. The hemopoietic changes observed appeared to parallel the increase in metabolism. The author believes that the thyroid gland has both a quantitative and a qualitative regulatory effect on the bone marrow.

144 Gilman, A., and Goodman, L. Pituitrin Anemia, *Nature*, London **143** 379, 1939.

145 Dohan, F. C., Jeffers, W. A., and Creskoff, A. J. Blood Pressure and Hematology in Dogs Injected with Anterior Pituitary Extract, *Proc. Soc. Exper. Biol. & Med.* **39** 327, 1938.

146 Jones, R. M. Human Sternal Marrow in Hyperthyroid and Myxedematous States, *Proc. Soc. Exper. Biol. & Med.* **41** 55, 1939.

IRON DEFICIENCY

Iron Metabolism and Experimental Anemia—The conditions under which iron may be absorbed from the alimentary tract continue to challenge investigation, particularly since the fundamental question of whether iron is received by the blood plasma and transported to certain tissues for storage irrespective of need or whether absorption of the metal is nicely adjusted to functional requirements has met varying replies from separate sources. Nevertheless, the conclusion seems warranted that the change in emphasis from investigations based on excreted iron to determination of the iron content of plasma and tissue after oral administration of the mineral marks a significantly progressive step in the acquisition of facts concerning iron metabolism.

Continuing their studies on iron in the blood, Moore and his associates¹⁴⁷ selected as subjects 16 healthy young women with relatively constant levels of erythrocytes and hemoglobin. They found that individual variations of the content of the iron serum ranged throughout the day and during a six month period from extremes of 0.01 to 0.065 mg per hundred cubic centimeters but that the changes followed no directional trend. With these normal subjects the values were unaffected by oral administration of liver or of medicinal iron. Studies of "nonhemoglobin blood iron" have been complicated by the presence of a fraction combined with the erythrocytes but dissociated from hemoglobin by the action of dilute acids or alkalis. The function of such "easily split-off" iron was not clearly understood until Barkan and Schales¹⁴⁸ demonstrated that this form of iron is probably derived from an intermediary compound formed during the breakdown of hemoglobin. Moore and his associates found that "easily split-off" iron varied in the same normal subject from 2.26 to 3.73 mg per hundred cubic centimeters.

Moore and his co-workers²⁶ observed the changes in iron content of the serum following oral administration of the metal to dogs and to patients with differing forms of anemia. They determined that absorption of iron from the gastrointestinal tract leads directly to increase in serum iron and that no intermediate rise in the iron content of the lymph of the thoracic ducts can be observed. Furthermore, in dogs the concentration of iron in the serum is directly proportional to the size of the oral dose until the quantities given exert local toxic effects or induce changes in intestinal motility. Ferrous compounds soluble in water effect comparable increases of serum iron in patients with appropriate types of

147 Moore, C. V., Minnich, V., and Welch, J. Studies in Iron Transportation and Metabolism. III. The Normal Fluctuations of Serum and "Easily Split-Off" Blood Iron in Individual Subjects, *J. Clin. Investigation* **18**: 543, 1939.

148 Barkan, G., and Schales, O. Chemischer Aufbau und physiologische Bedeutung des "leicht abspaltbaren" Bluteisens. dreizehnte Mitteilung in der Reihe der Eisenstudien, *Ztschr. f. physiol. Chem.* **248**: 96, 1937.

anemia, regardless of the degree of gastric acidity or its total absence. These authors also observed generally higher values for serum iron after administration of ferrous compounds than after its administration of iron in the trivalent form. The concomitant use of reducing agents, such as ascorbic acid and sodium formaldehyde sulfoxylate, appeared to enhance the absorption, as reflected by the serum iron, of both ferrous and ferric compounds, and this observation the authors interpret as further evidence that iron is absorbed largely, if not entirely, in the bivalent form. Bile pigment, chlorophyll and its derivatives, the secondary anemia fraction of liver and gastric mucin given in conjunction with iron failed to influence the subsequent serum increments of the metal. Of interest also is the demonstration by these authors of the apparently selective absorption of iron by patients with iron deficiency anemia as opposed to those with pernicious anemia, who already possess high concentrations of iron in the serum. It is the view of Moore and his colleagues that the hydrochloric acid of the stomach effects solution and ionization of iron salts and delays the subsequent formation in the intestine of insoluble and undissociated compounds. Furthermore, reducing substances in the intestine tend to retard the action of alkaline secretions in forming such physiologically inert iron compounds. Studies similar in scope are reported by Cosyns,¹⁴⁹ who gave ferrous and ferric salts containing equal amounts of iron to normal men and dogs and to pigs with nutritional anemia. He found that rises in the level of serum iron followed oral administration of ferrous compounds, whereas administration of the trivalent form of the metal led to little if any evidence of absorption.

Hemmeler¹⁵⁰ also has reported results of determinations of serum iron concentration. He found for healthy men a range of 100 to 130 micrograms of iron per hundred cubic centimeters and for menstruating women a range of 80 to 100 micrograms, but the values for nonmenstruating women equaled those for men. He determined the level of serum iron in cases of various types of anemia and found low values, such as 38 micrograms per hundred cubic centimeters, in cases of achylia gastrica and high levels, such as 218 micrograms per hundred cubic centimeters, in cases of pernicious anemia. Appropriate therapy resulted in normal values for serum iron. On the basis of his observations of serum iron in conditions associated with jaundice Hemmeler concluded that the liver plays an important part in the secretion of iron and that its role in the mechanism of regulation of iron is more important than that of the intestine.

149 Cosyns, H. Etude comparée des courbes de résorption des sels ferreux et des sels ferriques, *Compt rend Soc de biol* **130** 786, 1939.

150 Hemmeler, G. Serumeisen und Eisentherapie, *Schweiz med Wchnschr* **69**:316, 1939, *Serumeisen und Leber*, *Klin Wchnschr* **18** 1245 1939.

An investigation by Jenkins and Thomson¹⁵¹ of what they designate as nonhemoglobin cellular iron included 110 determinations in 24 cases of anemia. One might assume that the fraction with which they were concerned is identical with the "easily split-off" iron of Baikan, but their method for its estimation, involving determinations of the total iron content of the blood and subtraction from this figure of the calculated amount of hemoglobin iron based on a colorimetric hemoglobin determination, is open to several serious objections. Their results indicate that the "nonhemoglobin cellular iron" represents from 7 to 49 per cent of the total iron content of blood, the higher values occurring in the presence of severe anemia. This finding is attributed by the authors to a hypothetical compensatory mechanism which retains erythrocytes in the circulation beyond their normal span of survival, with consequent breakdown of some of the hemoglobin to intermediate iron-containing compounds.

The older view of a specific iron excretory function of the colon, which has been largely disestablished by the work of Widdowson and McCance and others, was reinvestigated by Maddock and Heath¹⁵². They performed colonic explants on the abdominal walls of 4 dogs and administered iron by mouth and by injection to these animals and to others, which had not been operated on. They obtained no evidence by histologic examination and qualitative tests for iron that the metal can be observed in process of excretion by any part of the alimentary tract in situ or by colonic explant. Their work supports the view that whatever iron may be excreted by the bowel is an extremely small amount.

More extensive studies of the behavior of radioactive iron are reported by Hahn and his associates¹⁵³ and by Manwaring¹⁵⁴. Employing standardized anemic dogs, Hahn and his group ascertained that the need for iron determines its absorption, so that under ordinary circumstances the requirement for excretion is explicable small. However, they fail to share the view that absorption of iron depends on differences in gradient between intestinal concentrations and plasma or lymph concentrations of the metal. They agree that iron is transported by the plasma, and they report detection of radioactive iron in circulating erythrocytes in an almost incredibly short time, amounting in some instances to but a few hours after absorption. Such iron is also found in mobilizable form in the liver, spleen and bone marrow. In the same

151 Jenkins, C. E., and Thomson, M. L. The Non-Haemoglobin Cellular Iron in Anaemia, *Brit J Exper Path* **19** 417, 1938.

152 Maddock, S., and Heath, C. W. Is Iron Excreted by the Gastro-Intestinal Tract of the Dog? *Arch Int Med* **63** 584 (March) 1939.

153 Hahn, P. F., Bale, W. F., Lawrence, E. O., and Whipple, G. H. Radioactive Iron and Its Metabolism in Anemia, *J Exper Med* **69** 739, 1939.

154 Manwaring, W. H. Metabolism of Radioactive Iron, *California & West Med* **51** 293, 1939.

laboratory¹⁵⁵ radioactive 'labeled' iron (the radioactive portion forms an infinitesimal fraction of the total dose) was injected intravenously into dogs in the form of ferrous gluconate. The initial extra output in urine and feces during a period of three to fifteen days ranged from 2 per cent to 8 per cent of the iron injected. For an indefinite period after intravenous administration of 100 to 250 mg the feces contained measurable amounts of radioactive "labeled" iron varying from 0.05 to 0.4 mg per day. Destruction of erythrocytes by acetylphenylhydrazine caused a definite increase in the 'labeled' iron eliminated in the feces probably through the increased iron content of the bile. In dogs the bile usually contributes very little iron to the intestinal contents (about 0.01 mg per day). The Rochester investigators conclude that the body controls its iron stores by absorption or lack of it rather than by its capacity to eliminate the metal. The dog excretes iron with difficulty and in small amounts, even in the plethoric state, by means of the biliary and gastrointestinal tracts.

Hahn and Whipple¹⁵⁶ were able to limit the production of hemoglobin by their standardized dogs by means of restriction of dietary protein even when excessive amounts of iron were given by mouth and by vein. They found that under the stress of protein limitation the proteins of salmon muscle, banana and carrot were well utilized and that the ratio of dietary protein to hemoglobin production was 7 or 8 Gm to 1 Gm. Whipple and Robschert-Robbins¹⁵⁷ observed the effect of spontaneous nephritis on the hemoglobin production of anemic dogs. In the early stages of the disease little or no effect is manifest. During more advanced nephritis there may be no change or a moderate decrease in production of hemoglobin. In such cases the average amounts to 70 per cent of the normal production. They conclude that spontaneous anemia in the nephritic dog cannot be expected to result from this degree of impairment of hemoglobin production.

Using Whipple's method of preparing anemic and iron-depleted dogs by repeated bleeding Wigodsky and his collaborators¹⁵⁸ found that commercial preparations of gastric mucin stimulated production of hemoglobin by amounts 55 to 70 per cent greater than could be accounted for by the quantities of iron present in the preparation.

155 Hahn, P. F., Bale, W. F., Hettig, R. A., Kamen, M. D., and Whipple, G. H. Radioactive Iron and Its Excretion in Urine, Bile and Feces. *J. Exper. Med.* 70:443, 1939.

156 Hahn, P. F., and Whipple, G. H. Hemoglobin Production in Anemia Limited by Low Protein Intake. *J. Exper. Med.* 69:315, 1939.

157 Whipple, G. H., and Robschert-Robbins, F. S. Nephritis and Its Influence upon Hemoglobin Production in Experimental Anemia. *J. Exper. Med.* 69:485, 1939.

158 Wigodsky, H. S., Bussabarger, R. A., and Fogelson, S. J. The Effect of Gastric Mucin on the Hemoglobin Regeneration in Anemic Dogs. *J. Lab. & Clin. Med.* 25:13, 1939.

Gastric mucin, however, in their studies was not as effective a stimulus to new hemoglobin formation as was beef liver

Fouts and his associates¹⁵⁹ produced hypochromic and microcytic anemia in 3 adult dogs by means of diets lacking in factor I, believed to be identical with vitamin B₆, or the rat antidermatitis factor. The anemia was not relieved by iron but was cured by the addition of crystalline factor I. These observations are believed by the authors to confirm their earlier conclusion that the antianemia factor of dogs and the antidermatitis factor of rats are identical.

Gueriant and Hogan¹⁶⁰ induced milk anemia in growing rats and subsequently fed the animals diets containing deaminized casein. The anemia persisted and could not be relieved by supplements of individual essential amino acids. Of the proteins examined, casein proved to be the most potent source of the antianemia agent. Lactalbumin and corn and wheat gluten were relatively ineffective. Corner¹⁶¹ reported additional observations on the pine disease (cobalt deficiency anemia) prevalent among sheep and cattle in certain parts of Scotland. He found that 1 mg. of cobalt daily for fourteen days cures the disease in sheep and prevents its recurrence for at least six months. Latsky¹⁶² confirmed the work of the Wisconsin investigators on the importance of copper as a supplement to iron in the treatment of milk anemia of growing rats. He was able to obtain reproduction of rats receiving a milk diet supplemented only by iron and copper.

Hypochromic Anemia of Adults—Anemia dependent on bleeding peptic ulcer has received a considerable amount of attention in respect to rate of blood regeneration, because it is unique among hypochromic anemias in its high incidence, its known and remediable causation and the opportunities for its prolonged observation under strict dietary and medicinal management. Lyons and Brenner¹⁶³ have reviewed the records of 237 cases observed at the Peter Bent Brigham Hospital between 1913 and 1936. Values for hemoglobin were not considered, but the weekly rate of erythropoiesis was determined in 177 cases on the basis of the lowest erythrocyte count. Apparently, speed of regen-

159 Fouts, P. J., Helmer, O. M., and Lepkovsky, S. Cure of Microcytic Hypochromic Anemia in Dogs with Crystalline "Factor I," *Proc. Soc. Exper. Biol. & Med.* **40** 4, 1939.

160 Guarrant, R. E., and Hogan, A. G. Effect of Amino Acids on Anemia Caused by Deaminized Casein, *J. Biol. Chem.* **128** 363, 1939.

161 Corner, H. H. Cobalt as a Factor in the Control of Nutritional Anaemia, *Brit. M. J.* **2** 169, 1939.

162 Latsky, J. M. Haematological Studies in Nutrition, *South African M. J.* **13** 461, 1939.

163 Lyons, R. H., and Brenner, C. Erythropoiesis Following Bleeding Peptic Ulcer, *Am. J. M. Sc.* **198** 492, 1939.

eration depended on the current degree of anemia present, regardless of the duration of the illness or the initial severity of the anemia. The rate of increase of erythrocytes in their cases, in which the patients were treated for the most part by a Sippy regimen, equaled that reported for patients receiving a liberal puréed diet and iron (Meulengracht, Schmid). The authors also came to the conclusion, held by some others, that beyond the actual increment of donated cells transfusion appeared to have no effect on the rate of erythropoiesis. In comment, it may be pointed out that a fallacy is involved in grouping patients with bleeding peptic ulcer without careful analysis of the case history and the nature of the anemia, since the extent of depletion of iron and other materials required for blood formation, depending largely on the duration of bleeding, may be expected to influence the rate of formation of red blood cells.

Pohle and Heath¹⁶⁴ report that administration by mouth of acid and alkaline salts to patients with hypochromic anemia treated by parenteral administration of iron failed to influence the rate of regeneration of hemoglobin, although changes in plasma volume were induced by altering the hydrogen ion concentration of the blood. They obtained an average of 70 per cent utilization of iron injected intramuscularly in new hemoglobin formation.

Determinations of the ascorbic acid content of the blood plasma were made by Alt, Chinn and Farmer¹⁶⁵ for 44 patients with achlorhydria associated with pernicious anemia or iron deficiency anemia. In the case of persons whose dietary histories indicated adequate intake of vitamin C, the ascorbic acid content of the blood was decreased from 0.87 mg per hundred cubic centimeters, the average for normal persons, to 0.57 mg, the average for patients with pernicious anemia. When the diet had been deficient in vitamin C the value for normal persons was 0.64 mg, for persons with pernicious anemia 0.47 mg and for those with iron deficiency anemia 0.45 mg per hundred cubic centimeters. The authors suggest various factors to which these relatively low values may be attributed, namely, destruction of vitamin C in alkaline gastric juice, destruction by bacteria and malabsorption.

Five cases of hypochromic anemia occurring in men are reported by Thiele¹⁶⁶. The age range was 14 to 49 years. Two of the patients

164 Pohle, F. J., and Heath, C. W. The Influence of Acid and Alkaline Salts upon the Blood in Hypochromic Anemia Treated by Iron Parenterally, *Am J M Sc* **197** 437, 1939.

165 Alt, H. L., Chinn, H., and Farmer, C. J. The Blood Plasma Ascorbic Acid in Patients with Achlorhydria (Pernicious and Iron Deficiency Anemia), *Am J M Sc* **197** 229, 1939.

166 Thiele, W. Ueber Anämien vom Typ der essentiellen Hypochromanämie bei Männern, *Deutsche med Wchnschr* **65** 208, 1939.

had complete anacidity. In all cases a history was obtained of rickets in childhood, or osseous deformities suggestive of infantile rickets were apparent. The author suggests that deficient mineral endowment before birth may play a part in the subsequent development of both rickets and iron deficiency anemia. Two cases of achlorhydric hypochromic anemia associated with peripheral neuritis are reported by Worster-Drought and Shafar⁴⁸. In 1 the patient was a man of 74 whose anemia was attributed to bleeding hemorrhoids, and in the other the patient was a woman of 51 in whom the condition followed partial gastric resection for ulcer of the stomach. The authors report that the objective neurologic findings improved after iron therapy and recovery from the anemia, but the possible influence of a deficiency of the vitamin B complex does not appear to have been sufficiently considered.

Changes in the blood following operations on the stomach were observed by Fravi¹⁶⁷ and by Dreher¹⁶⁸. The former found 16 instances of anemia, primarily hypochromic, among 50 patients who had undergone various degrees of resection of the stomach. The latter author reports the hematologic values in 101 cases two to eleven years after partial gastric resection. Of these, the erythrocyte count was less than 4,500,000 per cubic millimeter in 50 cases, and the color index was greater than 1 in 60 cases and below 1 in 29. In 40 cases the mean diameter of the erythrocytes was above 7.8 microns, and in 60 the reticulocyte percentage was above 5. Thirteen patients were found to have anemia associated with an increased red cell diameter, a high color index and an elevated reticulocyte percentage. The syndrome, including anemia, frequently resulting from removal of parts or all of the stomach is reviewed from both clinical and experimental points of view by Lejoux and Vermes⁵². The authors emphasize the relation between gastroduodenal function and hemopoiesis.

In a discussion of the treatment of iron deficiency anemia, Fowler and Baier¹⁶⁹ conclude that administration of inorganic ferrous compounds is preferable to the use of other iron preparations. So far as effect on hemopoiesis is concerned, they find no indications for the employment of such supplements to medicinal iron as extracts of liver, vitamins or other metals. Similar conclusions are arrived at by Whitby¹⁷⁰. In discussing the mechanism of production of iron defi-

167 Fravi, G. G. Ueber Sekretions- und Blutveränderungen nach Magenoperationen, *Schweiz med Wchnschr* **69** 174, 1939.

168 Dreher, M. Veränderungen des roten Blutbildes nach Magenresektion, *Ztschr f klin Med* **136** 525, 1939.

169 Fowler, W. M., and Baier, A. P. The Treatment of Iron Deficiency Anemias, *J A M A* **112** 110 (Jan 14) 1939.

170 Whitby, L. E. N. Advances in Anaemia and Blood Diseases, *Practitioner* **143** 391, 1939.

ciency, Delachaux¹⁷¹ emphasizes the importance of digestive disturbances leading to impaired absorption of iron and failure to utilize iron after its absorption. When the latter condition is present the author believes that liver extracts, manganese and copper may be of value.

Nutritional Anemia of Children—The subject of iron metabolism in infancy has been reviewed by Wallgren,¹⁷² who also reports his own studies on balance, carried out during the first year of life with infants born prematurely. He concludes that the anemia of premature infants, prevalent during the first two or three months, results from increased destruction of blood and is not related to iron deficiency. He found no evidence of functional incapacity of the marrow in such cases, except possibly a relative one due to the demands incident to rapid increase of blood volume. The need for new blood with its associated demands for blood-forming materials, especially iron, is responsible in large part for the lower values for erythrocytes and hemoglobin which persist in the case of premature infants after the period of postfetal hemolysis. But also of importance, according to the author, are the effects of exogenous factors on utilization of blood-building substances. Such factors, especially common among premature babies, include dietary errors and infections.

Josephs¹⁷³ studied the intake and output of iron of normal infants and found evidence of approximately 60 per cent absorption of dietary iron. Retention was decreased during infections and in infants not receiving vitamin D. The influence of infection may, however, be attributed to diminished intake of food. Josephs found that retention of iron tends to be above the average in cases of anemia even when the level of hemoglobin is falling, an observation which appears to be opposed to the usual concept of iron deficiency anemia and suggested to the author that "avidity of the tissues for iron might be a factor in the production of anemia." It is concluded that availability of tissue iron is important in the consideration of iron deficiency as a cause of anemia.

In a study of the utilization of medicinal iron, Josephs¹⁷⁴ found that retention was enhanced when the daily intake exceeded 2 mg per kilogram of body weight. The iron balance became negative when the total amount taken into the alimentary tract was approximately 0.1 mg

171 Delachaux, A. Remarques au sujet de la conduite thérapeutique dans les anémies par manque de fer, *Rev. med. de la Suisse Rom.* **59** 278, 1939.

172 Wallgren, A. Le fer dans la nutrition de l'enfant. Recherches sur le métabolisme du fer chez les enfants prématurés, nourris au sein, pendant la première année de leur existence, *Rev. franç. de pédiat.* **15**:117, 1939.

173 Josephs, H. W. Iron Metabolism in Infancy. I. Factors Influencing Iron Retention on Ordinary Diets, *Bull. Johns Hopkins Hosp.* **65** 145, 1939.

174 Josephs, H. W. Iron Metabolism in Infancy. II. The Retention and Utilization of Medicinal Iron, *Bull. Johns Hopkins Hosp.* **65** 167, 1939.

per kilogram per day Greater retention of medicinal iron occurred in anemic infants than in those with a normal blood picture Supplementary administration of copper appeared to increase the total utilization of medicinal iron but had little effect on the rate of utilization, it exerted no influence on retention of iron For several days after institution of iron therapy, storage of the metal preceded its utilization In anemic infants the percentage of retained iron utilized for hemoglobin production varied inversely with the amount retained When 2 mg or less per kilogram per day was retained the utilization was approximately 100 per cent The author compares this to the high degree of utilization of injected iron, which he attributes to a dose of less than 2 mg per kilogram

According to Josephs, after a period of medicinal iron therapy the increase in hemoglobin continues for about two to three weeks, and then the values remain stationary even though all the retained iron has not been used and the level of hemoglobin has not attained normal limits He concludes that medicinal iron possesses an important regulatory function in iron metabolism and erythropoiesis apart from its role as a "building stone" for hemoglobin

The possible relation of lowered secretion of acid by the stomach to the nutritional anemia of infants and young children has been studied by Wilson¹⁷⁵ In 12 cases of hypochromic anemia in young children he found 8 children with achlorhydria and 4 with hypochlorhydria after stimulation with alcohol or histamine Treatment with hydrochloric acid, 1 to 2 cc of a 10 per cent solution every four hours for seven to fourteen days, failed to elicit a reticulocyte response Good therapeutic results were obtained from administration of iron as ferrous sulfate in a dose ranging from 0.65 to 2 Gm daily

The value of a concentrated syrup made from cane sugar has been emphasized by Wilbar¹⁷⁶ in discussing the prevention of nutritional anemia in infants He found an average value for hemoglobin for 242 children residing on a sugar plantation in Hawaii of 9.8 Gm per hundred cubic centimeters in 1936 Subsequently (in 1938), after the molasses supplement had been used, the average value for hemoglobin was 12.6 Gm The cane sugar syrup contained iron ranging from 1 to 3 mg, and copper averaging 0.2 mg, per hundred cubic centimeters The relatively high value for copper may be attributed to the preparation and concentration of the syrup in copper kettles As a more or less complete dietary adjunct to milk in the feeding of young infants,

175 Wilson, R The Relation of Achlorhydria to the Nutritional Anaemia of Children, *Canad M A J* **41** 176, 1939

176 Wilbar, C L, Jr A New Carbohydrate for Prevention of Nutritional Anemia in Infants Preliminary Report, *Am J Dis Child* **58** 45 (July) 1939

Takuma and Sakurai¹⁷⁷ advocate soy bean meal. The product is a rich source of protein and in this respect compares favorably with casein, possessing a high content of the essential amino acids tryptophan and histidine. It also contains unsaturated fat and vitamins A and D and is especially well supplied with the B complex. Furthermore, soy bean meal is relatively rich in iron and copper. Infants with nutritional anemia improved rapidly when soy bean meal was added to the diet in amounts of 26 to 42 Gm daily for the age group between 1 and 10 months and in quantities between 400 and 600 Gm daily for older children. According to Lesné and Briskas,¹⁷⁸ mobilization of tissue iron is facilitated by administration of copper salts.

Hutchison¹⁷⁹ studied 300 infants in the first year of life. He found abnormally low values for hemoglobin in 26 per cent of breast-fed infants and in 35 per cent of those receiving cow's milk formulas. He concluded that the important etiologic factors of the nutritional anemia of infancy are undue prolongation of an exclusive milk diet, low birth weight and persistent infection. As a preventive measure he recommends administration of iron and ammonium citrates, 0.3 to 0.6 Gm daily, or the use of diet supplements to which iron has been added. Eight hundred and eighty-three rural school children in Florida were examined by Abbott and Ahmann,¹⁸⁰ who found hemoglobin levels of less than 9.64 Gm per hundred cubic centimeters in 50 per cent. An additional 31 per cent had concentrations below 11.7 Gm. Iron and ammonium citrates, 1 Gm three times a day, gave good results in spite of inadequate diet or hookworm infestation. Diets well supplied with foods high in iron content failed to influence subnormal values for hemoglobin after ninety days of use.

The subject of nutritional anemia of infancy and childhood has been reviewed by Smallwood¹⁸¹ and by Moore¹⁸². The latter emphasizes the value of the ferrous salts of iron and advocates their use without copper or liver fraction supplements. Parenteral administration of iron is recommended only in cases of persistent diarrhea.

177 Takuma, T, and Sakurai, K. Ueber die blutbildende Wirkung des Sojamehls, *Monatschr f Kinderh* **79** 62, 1939.

178 Lesné, E, and Briskas, S. B. Le traitement cuprique des anémies par carence alimentaire chez le nourrisson, *Médecine* **19** 618, 1938.

179 Hutchison, J. H. Nutritional Anaemia in Industrial District, *Arch Dis Childhood* **13** 355, 1938.

180 Abbott, O. D., and Ahmann, C. F. Iron Deficiency Anemia in Children, *Am J Dis Child* **58** 811 (Oct) 1939.

181 Smallwood, W. C. The Anaemias of Infancy and Childhood, *Practitioner* **142** 453, 1939.

182 Moore, C. V. Nutritional Anemias of Infancy and Early Childhood, *Ohio State M J* **35** 25, 1939.

Anemia of Pregnancy—An understanding of the physiologic variations of the blood in pregnancy is essential to accurate analysis and interpretation of pathologic observations. As yet, however, such knowledge is decidedly incomplete. A number of studies have been recently reported of the changes occurring in the blood in apparently healthy pregnant women. Unfortunately, however, some of the work is open to question because of apparent technical errors and inaccurate calibration in the measuring of hemoglobin.

The hematologic values for 1,000 private obstetric patients are reported by Eskridge and Serwer¹⁸³. The data are difficult to interpret because of the method of presentation, but the lowest range of erythrocyte counts was between 3,000,000 and 3,500,000 per cubic millimeter and represented, apparently, 5.1 per cent of the patients observed during the first trimester, 7.8 per cent during the second trimester and 16.4 per cent during the last three months of gestation. The lowest range of hemoglobin levels was between 10.2 and 11.9 Gm per hundred cubic centimeters and represented 15.8 per cent of the patients in the first trimester, 15.5 per cent in the second and 38.0 per cent in the third. However, the values for hemoglobin appear to be generally too high in comparison with the erythrocyte counts, possibly because of the use of inaccurate calibration in an older method of determination.

The effect of pregnancy on the blood picture was studied by Kenyon and Macy,¹⁸⁴ who observed hourly physiologic variations in the counts. Many of their erythrocyte counts are, however, inexplicably low. Sternal marrow was aspirated from pregnant and nonpregnant women by Pitts and Packham.¹⁸⁵ Nucleated cell counts and differential counts were made, but the practice of the authors of removing 10 cc of so-called marrow leads to inclusion of such a disproportionate amount of circulating blood, probably at least 99 per cent, that quantitative statements concerning the composition of the marrow are open to question. The hematologic values for 525 pregnant women were determined by Gottlieb and Streat,¹⁸⁶ Of these, 275 received no antianemia therapy, and 250 were given various preparations of iron. The blood of the infants was studied in 100 cases. Among the untreated patients the average values for hemoglobin during the three trimesters were respectively

183 Eskridge, J. B., Jr., and Serwer, M. J. Blood Studies in Private Obstetrical Patients, *South M J* **32** 24, 1939.

184 Kenyon, F., and Macy, I. G. Hourly Physiologic Variations in Peripheral Hemoglobin, Red and White Counts of Women. Effect of Pregnancy upon Blood Counts, *Human Biol* **10** 511, 1938.

185 Pitts, H., and Packham, E. A. Hematology of Sternal Marrow and Venous Blood of Pregnant and of Non-Pregnant Women, *Arch Int Med* **64** 471 (Sept.) 1939.

186 Gottlieb, R., and Streat, G. J. The Prevention of Maternal and Infant Anemia, *Surg, Gynec & Obst* **68** 869, 1939.

11.2 Gm, 10.5 Gm and 9.1 Gm per hundred cubic centimeters. A similar decline in the level of hemoglobin did not occur in the non-treated group. Iron and ammonium citrates, reduced iron, ferrous sulfate with vitamin B complex and ferrous carbonate with copper were employed. All yielded good results, and no advantage seemed to attend the use of the two last-named, "supplemented" preparations. The authors made the interesting observation that the infants of untreated mothers at birth possessed an average erythrocyte level of 7,000,000 per hundred cubic centimeters and a hemoglobin concentration of 16.8 Gm, whereas the values for infants of the treated group were, respectively, 5,290,000 per cubic millimeter and 15.44 Gm. However, after thirty-two weeks the average red cell count for the infants of untreated mothers was 2,860,000 per cubic millimeter, and the hemoglobin content averaged 7.14 Gm, whereas the respective values for the infants of mothers who had received medicinal iron during gestation were 4,300,000 per cubic millimeter and 11.48 Gm.

A study of the effect of administration of iron on the level of hemoglobin during pregnancy was carried out by Widdowson¹⁸⁷. Hemoglobin estimations only were done. The progressive decline which characterized the values for hemoglobin in her cases was converted into a rise by administration of either reduced iron or iron and ammonium citrates. However, after withdrawal of iron the values for hemoglobin fell at approximately the rate observed before institution of iron therapy. According to the author's previously expressed views on iron absorption and excretion, an excess of the metal should have been stored during the period of its administration. Failure of utilization of such stored iron is attributed by her to lack of stimulus to the marrow, and she believes that such incitement to hemopoietic activity may depend on high values for plasma iron. However, in the absence of erythrocyte counts and determinations of cell volume, interpretation of Widdowson's data is difficult.

Standards for normal minimal values during pregnancy have been set by Labate¹⁸⁸ at 4,000,000 per cubic millimeter for erythrocytes and 11.6 Gm for hemoglobin. According to these criteria, he found a 48 per cent incidence of anemia among 881 pregnant women. The prevalence of anemia of the macrocytic type was notable. Dietary deficiencies appeared to exert an especially great effect on the blood picture in cases of prenatal complications. Three hundred and twenty-five of Labate's patients were given ferrous sulfate, 0.32 Gm three times a day. At delivery the average erythrocyte count was 4,090,000 per

¹⁸⁷ Widdowson, E. M. Iron Administration and Haemoglobin Levels During Pregnancy, *Lancet* **2** 640, 1939.

¹⁸⁸ Labate, J. S. Classification and Treatment of Anemias of Pregnancy, *Am J Obst & Gynec* **38** 48, 1939.

cubic millimeter, and the average value for hemoglobin, 11.61 Gm. Three hundred and seven women were not given iron, and at delivery the average values for red cells and hemoglobin were respectively 3,010,000 per cubic millimeter and 8.16 Gm. Labate found a morbidity rate of 14.8 per cent among the treated patients as compared to a rate of 19.5 per cent in the untreated group. He concludes that "iron therapy must be continued beyond the period of hospital stay to have any significant effect on the erythrocytes and hemoglobin of the postpartum anemic patient."

Hemoglobin estimations and erythrocyte counts were done in the cases of 88 pregnant women at monthly intervals or oftener by Bourdillon and his associates¹⁸⁹. The patients were divided arbitrarily into two groups, and to the members of one was given iron and ammonium citrates, 4 Gm daily, whereas those of the other were untreated. An average decline in the concentration of hemoglobin from the fifth to the ninth month of 0.7 Gm per hundred cubic centimeters occurred in the untreated group, and an average increase of 1.15 Gm was observed among those receiving iron. The authors state in respect to their cases that "multiple pregnancies, age, and poverty were all associated with a low hemoglobin, but which, if any, was the dominant factor could not be determined."

Tentative standards of normality for the blood in pregnancy were formulated by Bethell, Gardiner and MacKinnon¹⁹⁰. The mean and minimum levels were based on data obtained at monthly intervals during gestation from 30 women. The criterion for selection of the cases was return in each instance to the normal range of values for nonpregnant women at the seventh week after delivery in the absence of antianemia therapy or change in dietary habits. The minimum normal values adopted for nonpregnant women were erythrocytes, 4,130,000 per cubic millimeter, hemoglobin, 12.17 Gm and packed cell volume, 37.5 per cent. All determinations were made in duplicate with oxalated venous blood, with certified instruments and standardized methods. The lowest values were found at the beginning of the seventh month, when the red cell count sometimes fell to a level of 3,500,000 per cubic millimeter and the hemoglobin content to 10.1 Gm. The authors were unable to attribute the physiologic decline in values during pregnancy solely to dilution of the plasma, since during the first trimester of pregnancy a uniform decrease in the mean corpuscular hemoglobin was observed and in the second trimester an increase in the mean corpuscular volume was noted. On the basis of such standards of normality an

189 Bourdillon, J. F., Cargill, D. R., Cosh, J., and Miles, J. A. R. Mild Anaemias in Pregnancy, *St. Thomas's Hosp. Rep.* **3**, 89, 1938.

190 Bethell, F. H., Gardiner, S. H., and MacKinnon, F. The Influence of Iron and Diet on the Blood in Pregnancy. *Ann. Int. Med.* **13**, 91, 1939.

incidence of 53.8 per cent of true anemia was observed in 158 clinical cases studied. In 26 per cent the anemia was hypochromic and either normocytic or microcytic, in 15.2 per cent it was orthochromic and macrocytic, and in 12 per cent it was hypochromic and macrocytic. Anemia in the first group was attributed solely to iron deficiency, in the second group it was attributed to dietary deficiencies related to inadequate intake of animal protein, and in the third group it was ascribed to a lack of both iron and protein. In a controlled series of clinical studies it was found that administration of ferrous sulfate alone in a dose of 0.32 Gm three times a day corrected anemia due to iron deficiency, improvement of the diet led to a satisfactory hemopoietic response in cases of nutritional deficiency, but the most satisfactory results were obtained in the latter group when institution of a diet adequate in protein was combined with administration of medicinal iron. It was also found that iron therapy given to a group of women with a presumably normal blood picture led to higher levels of hemoglobin after delivery than were observed in a group of untreated women with the same initial values.

Cases of pernicious anemia of pregnancy are reported by Dor,¹⁹¹ Onhausen and Mitchell⁶⁴ and Ritter and Crocker.¹⁹² The last-named authors describe a case of severe macrocytic anemia of pregnancy with suboptimal response to parenteral liver extract and the subsequent development of a similar macrocytic anemia in the infant. After delivery the blood of the mother returned to normal, and the infant gradually recovered, although not demonstrably as the result of administration of liver extract, medicinal iron or vitamin C.

A case of erythroblastic splenomegaly occurring in a young Negress during pregnancy was reported by Moore and Pastore.¹²⁰ At autopsy extramedullary erythropoiesis was observed, but the bone marrow was said to be normal. No explanation was given for the disturbance in erythrocytic tissue except the suggestion that it may have followed one of the commoner forms of anemia of pregnancy.

An experimental study of the effect of maternal diet supplements on the size of the erythrocytes of newborn rats was carried out by Briese and Higgins.¹⁹³ Twenty per cent (by weight) of desiccated hog stomach (ventriculin) was added to the standard ration for varying periods during gestation. The size of the red cells was determined by measur-

191 Dor, P. L'anémie pernicieuse gravidique, réflexions à propos de deux observations, *Bull. med.*, Paris **53** 571, 1939.

192 Ritter, J. A. and Crocker, W. J. Macrocytic Anemia of Pregnancy and Anemia of the Newborn, *Am. J. Obst. & Gynec.* **38** 239, 1939.

193 Briese, E., and Higgins, G. M. The Effect of Feeding Ventriculin to Pregnant Rats, with Special Reference to the Size of the Red Blood Cells of the Young, *Anat. Rec.* **73** 105, 1939.

ing the diameters of 100 cells from each sample. A total of 177 control rats was used, the offspring of mothers on standard unsupplemented diets, and the mean erythrocytic diameter was found to be 9.42 microns. One hundred and twenty-five newborn test rats were examined, and in general it was found that the litters of the mothers who had received ventriculin possessed red cells with smaller diameters than those of the controls. However, the range of results was wide. The authors conclude that maturation of the blood cells in the developing fetus is usually accelerated by addition of ventriculin to the maternal diet.

POISONING BY PHYSICAL AGENTS

Lead—To throw some light on the value of the "basophilic aggregation test" of infants as an evidence of lead poisoning, McCord and Bradley¹⁹⁴ studied the percentage of red blood cells showing this phenomenon in newborn animals and human beings. In the albino rat 71.7 per cent of the cells showed basophilic aggregations at birth, and in infants, 5.3 per cent revealed the same phenomenon. In the case of the latter the number diminished rapidly, reaching a level of 0.5 to 2.0 per cent by the eighth day. Thus beyond ten days an increase in the number of cells showing basophilia is of pathologic significance in infants. In young rats, however, a high percentage of erythrocytes containing basophilic substance persists until near the hundredth day of life, militating against the use of these animals in studying experimental lead poisoning.

In Gocher's¹⁹⁵ study of lead workers, he found that a count of over 2 stipple cells per 2,000 red blood cells indicates toxicity and absorption, the count being higher with the greater degrees of toxicity. With the variations in the cycle of lead excretion, stipple cells may appear or disappear from the circulation. Anemia may be absent (over 90 per cent [Sahli] hemoglobin) in cases of severe poisoning. Usually, when there is poisoning the reading is 68 per cent or less. When there is involvement of the liver the readings are usually from 65 to 70 per cent. Reticulocytes decrease in number with lessened exposures to lead, rising when the hygiene is faulty. The number is increased in patients with abdominal cramps and involvement of the nerves and in patients with impending toxemia from lead poisoning. The behavior of the reticulocytes seems to be independent of the stipple cells. A case of a man in apparently perfect health with 100 per cent reticulocytes is recorded.

194 McCord, C. P., and Bradley, W. H. Basophilic Aggregations in Blood of Newly Born. (a) Laboratory Animals, (b) Humans, *Am J Clin Path* **9** 329, 1939.

195 Gocher, T. E. P. Blood Examinations in Lead Poisoning, *Northwest Med* **38** 289 (Aug.) 1939.

The conditions present in early susceptibility to lead are summarized as follows 1 An increase in reticulocytes occurs in all cases 2 An increase in stipple cells occurs in about 25 per cent of the cases 3 A slight drop in diastolic pressure has been observed in 15 cases of "cramps" 4 The hemoglobin percentage and the number of red blood cells are usually not affected 5 There is slight leukocytosis, with a count of about 10,000 per cubic millimeter in most cases 6 At first there is an increase in neutrophils, to about 88 per cent at times 7 There is an increase in large mononuclear cells, to 10 or 12 per cent 8 There is an initial increase in eosinophils, to 4 to 10 per cent, and then a decrease occurs 9 Polychromatophilia is present in varying proportions in the red cells The blood picture and general health of patients suffering from lead poisoning were found by Holmes, Campbell and Amberg¹⁹⁶ to improve rapidly after daily ingestion of 100 to 200 mg of vitamin C The stipple cells disappeared from the blood stream, and the urinary excretion of lead was reduced to normal limits

Tompsett and Anderson¹⁹⁷ conclude that excretion of more than 100 micrograms of lead per hundred cubic centimeters of blood, or a total daily excretion of 1 mg or more, is indicative of lead poisoning In rabbits made anemic by prolonged injection of lead salts, Lourau, de Sacy and Arthus¹⁹⁸ found that blood regeneration could be stimulated by injection of liver extracts which were active in the treatment of pernicious anemia

Benzene—Erf and Rhoads¹⁹⁹ reported the changes in the blood of 9 patients with benzene poisoning Of these, 8 recovered, and 1 died of myelogenous leukemia The authors present evidence that the abnormal rate of destruction of blood may be one of the factors in the production of anemia in cases of benzene poisoning Hunter²⁰⁰ emphasizes the importance of evaluation of the entire blood picture in the early diagnosis of benzene poisoning Polycythemia, anemia, leukocytosis or leukopenia, leukemia or a leukemoid picture (myelogenous or lymphatic), eosinophilia, megalocytosis, microcytosis or immature elements in otherwise normal blood may characterize individual patients

196 Holmes, H N Campbell K, and Amberg, E J The Effect of Vitamin C on Lead Poisoning, *J Lab & Clin Med* **24** 1119, 1939

197 Tompsett, S L, and Anderson, A B Lead Poisoning Lead Content of the Blood and of Excreta, *Lancet* **1** 559, 1939

198 Lourau, M, de Sacy, G S, and Arthus, A Regenerations sanguines produites dans le saturnisme experimental par un facteur hepatoque hydrosoluble Generalite de la réaction, *Compt rend Soc de biol* **130** 642, 1939

199 Erf, L A, and Rhoads, C P The Hematological Effects of Benzene (Benzol) Poisoning, *J Indust Hyg & Toxicol* **21** 421, 1939

200 Hunter, F T Chronic Exposure to Benzene (Benzol) II The Clinical Effects, *J Indust Hyg & Toxicol* **21** 331, 1939

Mallory, Gall and Brickley ²⁰¹ note that in cases of chronic benzene poisoning the entire hemopoietic system is affected. The bone marrow may be hypoplastic but is more frequently hyperplastic. Extramedullary hemopoiesis is noted in some persons. Hyperplasia is noted only after long exposure, whereas hypoplasia may appear with either short or long exposure. Curiously, hyperplasia is noted more commonly in males, whereas hypoplasia is more common in females. Some of the extramedullary changes resemble neoplasms. Two cases of leukemia were observed, in 1 of which there was frankly neoplastic tumor formation.

Feller ²⁰² found that in rats the changes in the number of leukocytes in the peripheral blood and in the histologic structure of the tissues brought about by exposure to radium or to benzene were similar. However, there were many differences (eosinophil behavior, initial lowering of the absolute number of neutrophils and smaller variations in the number of erythrocytes and the hemoglobin percentage for the benzene-treated rats) that suggested a different mechanism in the action of the two agents. Recovery was more rapid after the injury from exposure to benzene. In workers with the rotogravure process in New York, Greenburg, Mayers, Goldwater and Smith ²⁰³ found serious abnormalities in the blood from benzene poisoning in the absence of definite clinical symptoms. The authors conclude that a reduction in the number of red blood cells and an increase in their size constitute a more sensitive and earlier sign of benzene poisoning than does a low leukocyte count. There is an enormous difference in individual susceptibility.

Oestreicher ²⁰⁴ found that yellow bone marrow was without effect on experimental benzene leukopenia in the rat. Thrombopenia with prolongation of the coagulation time of the blood is an initial and serious symptom in persons exposed to benzene, according to Mignolet ²⁰⁵. In the majority of the cases the anemia is of the aplastic, hyperchromic type. Eosinophilia is relative and not absolute. Granulocytopenia is definite evidence that the poisoning is present, but the patient may respond to

201 Mallory, T. B., Gall, E. A., and Brickley, W. J. Chronic Exposure to Benzene (Benzol). III. Pathologic Results, *J. Indust. Hyg. & Toxicol.* **21** 355, 1939.

202 Feller, A. Der Einfluss des Radiums und des Benzols auf das Blut und auf die blutbildenden Organe mit besonderer Berücksichtigung der Leukozyten, *Strahlentherapie* **60** 393, 1937.

203 Greenburg, L., Mayers, M. R., Goldwater, L., and Smith, A. R. Benzene (Benzol) Poisoning in the Rotogravure Printing Industry in New York City, *J. Indust. Hyg. & Toxicol.* **21** 395, 1939.

204 Oestreicher, F. The Influence of Yellow Bone Marrow Extract on Experimental Benzene Leucopenia, *Acta brev. Neerland.* **9** 260, 1939.

205 Mignolet, F. Les memopathies du benzol, *Sang* **13** 268, 1939.

infection with neutrophilic leukocytosis Penati and Vigliani²⁰⁶ found that patients with chronic benzene intoxication may show aplastic anemia with either aplastic or hyperplastic bone marrow and with occasional myeloid metaplasia in the liver and spleen as well as acute or chronic leukemia

Wallbach²⁰⁷ has summarized his previous publication on the action of benzene and thorium-x on the blood Lamy, Kissel and Pierquin²⁰⁸ describe 10 cases of industrial benzene poisoning Anemia, purpura and neutropenia were present in different patients In the cases of mild involvement there was an erythroblastic reaction while in the cases of severe involvement the patients were marked by myeloid aplasia with hyperplasia of the cells of the reticulo-endothelial system The prognosis is uncertain, and relapse may follow reexposure Examination of the blood and bone marrow gives data of value in judging the prognosis Repeated blood transfusions are of therapeutic value The authors advocate legislative measures to prevent industrial benzene poisoning

Other Agents—Additional light on the mechanism of action of the roentgen ray on bone marrow is shed by the work of Bertola, Ravetta and Zelaschi²⁰⁹ Roentgen therapy (210 to 630 r) was applied every other day to 4 normal persons and the same therapy (60 to 150 r) to 8 patients with myelogenous and lymphatic leukemia and to 2 patients with malignant lymphogranuloma The bone marrow was then studied from material taken by sternal puncture No changes were noted in the erythroblastic tissue after irradiation in the normal persons or in the patients In the leukoblastic tissue there appeared to be increased maturation of the cells, with fewer mitotic figures and prophases and more telophases In cases of malignant lymphogranuloma the changes were less marked These changes followed irradiation of either the bones or the spleen

Congo red does not exert a hemostatic action in normal persons, according to the experiments of Richardson²¹⁰ On intravenous injec-

206 Penati, F, and Vigliani, E C Sul problema delle mielopatie aplastiche e leucemiche da benzolo, *Rassegna di med appl lavoro indust* **9** 345, 1938

207 Wallbach, G Resume de mes examens compares concernant l'action du benzol et du thorium X sur les reactions leucocytaires, *Sang* **13** 719, 1939

208 Lamy, M, Kissel, P, and Pierquin, L La myelotoxicose benzolique Etude clinique et hematologique de dix cas d'intoxication professionnelle par le benzol, *Sang* **13** 467, 1939

209 Bertola, A, Ravetta, M, and Zelaschi, C Roentgen-irradiazione dei tessuti emopoietici in soggetti normali ed emopatici (modificazioni del midollo osseo) Nota preventiva, *Gazz d osp* **59** 1255, 1938

210 Richardson, A P Congo Red Hematologic Actions, *Am J M Sc* **198** 87, 1939

tion of large doses there is a slight temporary anemia with hemagglutination, an effect absent with small doses. Moderate leukocytosis (neutrophilia) and a marked increase in the sedimentation rate result. Congo red in dilutions of 1:1,000 protects the erythrocytes of man against hemolysis from hypotonic solution of sodium chloride, hypertonic urea and sodium taurocholate in saline solutions and saponin in dextrose and saline solutions.

Experimental chronic cadmium poisoning in albino rats was found to produce anemia at all levels of dosage in the work of Wilson and De Eds²¹¹. The severity of the anemia (type not stated) increased with the percentage of cadmium added to the diet.

Meulengracht and Lundsteen²¹² found that the gray-bluish violet cyanosis of acetanilid poisoning is due to a paranitrophenol derivative and not to methemoglobin. The anemia may be very severe, with a hyperplastic bone marrow involving all of the cellular elements. Recovery is rapid, following discontinuance of ingestion of the poison.

BLOOD IN NEPHRITIS

Bock and Weyand²¹³ found that the anemia associated with various types of nephropathy is the result of increased destruction (indicated by urobilin determinations) and deficient rate of formation of the red blood cells. The lack of reticulocytosis is attributed to rapid aging of the red blood cells or to retarded elimination from the bone marrow. Nephropathies are divided into "pale hypertension" (nephroangiosclerosis with a blood pressure of 213 systolic and 129 diastolic), and "red hypertension" (nephroangiosclerosis with a blood pressure of 180 systolic and 90 diastolic). In the former condition the total mass of red blood cells is reduced and the plasma volume is increased, but in the latter the cell and plasma volume are normal. In cases of "pale hypertension" the red blood cells are thin and pale and are small in volume but normal in diameter as compared with normal erythrocytes in cases of "red hypertension". The most important factor of increase in cell catabolism, Bock and Weyand conclude, is not impairment of erythrocytes in the presence of contracted vessels but retention of urinary waste products.

211 Wilson, R. M., and De Eds, F. Experimental Chronic Cadmium Poisoning, *Science* **90** 498, 1939.

212 Meulengracht, E., and Lundsteen, E. Die Cyanose und Anämie bei chronischer Acetanilid-Vergiftung, *Folia haemat* **63** 89, 1939.

213 Bock, H. E., and Weyand, L. Ueber Anämie bei Nierenkrankheiten, die Blutmauserung bei Kranken mit blassem Hochdruck und solchen mit Uebergangsformen vom roten zum blassen Hochdruck, *Deutsches Arch. f. klin. Med.* **184** 369, 1939.

Nolli²¹⁴ finds from sternal puncture of patients with nephritis that lesions of the bone marrow develop early. In the presence of renal sclerosis with anemia there is hypoplasia of the bone marrow. In the presence of acute diffuse hemorrhagic glomerulitis with anemia the marrow is of the type associated with posthemorrhagic anemia. In the presence of chronic renal inflammation the output of stem cells is diminished. Asemic, iron and liver extract are said to be of value early in the disease. Terminally, there is a gelatinous transformation of the marrow.

Loeper and Perreau²¹⁵ found anemia to be present in 12 to 15 per cent of cases of chronic nephritis. It is usually orthochromic, occasionally hypochromic and rarely hyperchromic. Leukocytosis appears in about half of the cases, occasionally with eosinophilia. Possible mechanisms for the anemia are dilution of the blood, food deficiency, hemolysis, toxic action of amines and inhibition of blood regeneration. Therapeutic measures include small blood transfusions, liver therapy, administration of extract of kidney, institution of a diet rich in vitamins and administration of tryptophan, pancreatic extracts and charcoal to reduce intestinal putrefaction.

Kobryner and Rozenkranc²¹⁶ consider that the elevation in the number of neutrophils in conditions accompanied with edema is associated with the increased density of the blood (concentration effect). There is a reduction in number of these cells with diuresis. Nephritis caused little or no change in hemoglobin production in cases of induced hemorrhagic anemia in the early stages of the disease in a group of dogs studied by Whipple and Robscheit-Robbins¹⁵⁷. In the late stages of nephritis there was no change or moderate change in hemoglobin regeneration as compared with that observed in "standard anemic dogs". The average production of hemoglobin was 70 per cent of the normal.

Ultrafiltrates of serum from patients with uremia, with renal insufficiency and with various other diseases associated with changes in blood chemistry were injected into rabbits by Marcolongo and Leone²¹⁷. Alterations of the hemopoietic organs, especially hemosiderosis of the spleen, parenchymal degenerations, leukocytic changes and specific alterations due to the anemia-producing properties of the uremic blood serum were noted. This "ultrafiltrate anemia" had no specific character-

214 Nolli, B. L'esplorazione funzionale del midollo osseo nelle nefriti, *Gior di clin med* **20** 1023, 1939.

215 Loeper, M., and Perreau, P. L'anemie brightique, *Sang* **13** 113, 1939.

216 Kobryner, A., and Rozenkranc, D. Sur la pseudo-leucocytose dans les états œdémateux, *Sang* **13** 870, 1939.

217 Marcolongo, F., and Leone, P. Tentativi di riproduzione sperimentale di anemie con ultrafiltrato di siero uremico, *Haematologica* **20** 49, 1939.

istics In some animals the volume and the diameter of the red blood cells were diminished, while in others both were increased The bone marrow picture was always that of "secondary" anemia

POLYCYTHEMIA

Émile-Weil, Isch-Wall, Peiles and Aschkenazy²¹⁸ present a comparative study of the material aspirated by sternal, splenic and hepatic punctures in a case of polycythaemia vera The greatest pathologic variation was noted in the marrow (hyperplasia of the erythropoietic tissue)

Reznikoff²¹⁹ summarizes the recent concepts of polycythemia, showing the thickening of the arterioles and capillary walls in the bone marrow and illustrating the use of acetylphenylhydrazine, venesection and roentgen rays by the spray technic in treating 3 patients

Various types of erythroblastic anemia have been described In Israel's²²⁰ case a 42 year old woman had an illness of several months' duration, characterized by splenomegaly, hepatomegaly, severe anemia, enormous numbers of normoblasts and megaloblasts in the blood and hyperplasia of these elements in the bone marrow Roentgen irradiation, liver, iron, arsenic and transfusions failed to prevent a fatal termination Israel eliminated leukoerythroblastic anemia, erythroblastic disease of adults, polycythaemia vera and a leukemoid condition and called the disease true erythremia analogous to leukemia

While true polycythemia is rare in children, polycythemia in various types may appear Kellman's²²¹ patient, a 6 year old girl, showed a temporary rise in the red blood cell count to 9,000,000 per cubic millimeter, with 77,500 leukocytes, of which 82 per cent were lymphocytes A spontaneous remission of three years' duration was in progress when the case was described

Schippers²²² studied 6 cases of polycythemia in infants ranging from a few days to 5 weeks of age Cerebral and cardiac anomalies were not the cause, as the polyglobulism disappeared after administration of oxygen There was no normoblastosis and no hemolytic icterus, suggesting retarded hemolysis Occasional symptoms were tumor of the

218 Emile-Weil, P, Isch-Wall, P, Peiles, S, and Aschkenazy Les ponctions couplees dans la polyglobulie simple (type Vaquez), Sang **13** 96 1939

219 Reznikoff, P Polycythemia, Bull New York Acad Med **15** 311, 1939, Polycythemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis, University of Wisconsin Press, 1939, p 207

220 Israels, M C G Immature Cell Erythraemia in an Adult, J Path & Bact **47** 299, 1939

221 Kellman, L Primary Polycythemia with Leukemic Manifestations, Am J Dis Child **58** 146 (July) 1939

222 Schippers, J C Polyglobulie prolongee apres la naissance Rev franc de pediat **15** 102, 1939

aim, hypertonia and somnolence, but some patients were asymptomatic. There was no recurrence of the disease.

Reifenstein²²³ describes a case of erythremia with gout evolving into aleukemic myelogenous leukemia with anemia. The bone marrow was hyperplastic and was regarded as typical of myelogenous leukemia.

Familial polycythemia was studied by Nadler and Cohn²²⁴ in the cases of 4 patients aged 11, 13, 16 and 18 years respectively. There was no leukocytosis, no increase in the basal metabolic rate and no evident splenomegaly, but the circulating cell mass was greatly increased, as in cases of polycythaemia vera.

Coronary thrombosis may be a complication of polycythaemia vera, as is illustrated by the cases reported by Miller²²⁵. Of 7 patients examined at autopsy, 3 had myocardial alterations with associated coronary occlusions, and 2 showed extensive similar changes in the heart muscle but no thrombus in the coronary tributaries, while 2 showed no myocardial damage or myocardial thrombosis. The similarity of precordial pain in polycythemia and anemia is noted.

Thrombophlebitis of the hepatic veins secondary to polycythaemia vera was noted in Altschule and White's²²⁶ patient.

In cases of polycythemia, Émile-Weil, Aschkenazy and Capron²²⁷ found that the elevated glutathione content is associated with the degree of polyglobulism, with wide variations in the oxidized form. The value for total glutathione in cases of polycythemia varied from 49.4 to 91.1 mg per hundred cubic centimeters, that for reduced glutathione, from 44.7 to 91.0 mg, and that for oxidized glutathione, from 0 to 9.3 mg.

Vogelensang²²⁸ found very high values for zinc in the blood of a patient with polycythemia.

Davis²²⁹ found that the polycythemia produced in dogs by exposure to low atmospheric pressures, as well as that caused by exercise or cobalt

223 Reifenstein, G. M. A Case of Erythremia, Gout and Subleukemic Myelosis, *Am J M Sc* **197** 215 (Feb.) 1939.

224 Nadler, S. B., and Cohn, I. Familial Polycythemia, *Am J M Sc* **198** 41, 1939.

225 Miller, H. R. The Occurrence of Coronary Artery Thrombosis in Polycythemia Vera, *Am J M Sc* **198** 323, 1939.

226 Altschule, M. D., and White, G. Chiari's Syndrome in Patient with Polycythemia Vera. Report of Case, *New England J Med* **220** 1030, 1939.

227 Émile-Weil, P., Aschkenazy, A., and Capron, I. Le glutathion sanguin dans les polyglobulies, les leucémies et les érythroblastoses chroniques, *Sang* **13** 705, 1939.

228 Vogelensang, E. H. Occurrence of Zinc in Human Blood, *Pharm Weekbl* **76** 89, 1939.

229 Davis, J. E. Depression of Polycythemia by Choline Hydrochloride, *Proc Soc Exper Biol & Med* **40** 445, 1939, Depression of Experimental Polycythemias by Choline Hydrochloride or Liver Administration, *Am J Physiol* **127** 322 1939.

chloride, could be reduced and the blood restored to the normal level by oral administration of 8 mg of choline hydrochloride per kilogram of body weight per day. A similar effect could be produced by the feeding of raw hog or beef liver in amounts of 75 Gm per day. Choline chloride did not affect the erythrocyte count of normal dogs. The author concludes that the choline content of raw liver is the effective agent and suggests that it may be of value in the treatment of polycythaemia vera.

In normal unanesthetized dogs, Palitz²³⁰ found that artificial fever of an hour's duration caused an increase in erythrocyte count, hematocrit volume and concentration of serum protein. This reaction was absent after the spleen was removed.

While the blood volume may be 60 to 70 per cent below normal in cases of anemia due to chronic loss of blood, nephritis or hemolysis or in cases of "idiopathic" hypochromic anemias, Gibson, Harris and Swigert²³¹ found that there is a great increase in the total blood volume in cases of polycythaemia vera. This is due to the increase in cell volume, the plasma volume remaining normal. Repeated phlebotomies reduced the cell volume and hence the total volume, as the plasma volume remained unchanged.

Polycythemia was produced in rats by the feeding of fresh or acetone-extracted pituitary glands by Flaks, Himmel and Zotnik²³². A similar polyglobulism was noted in some hypophysectomized animals as well as in those treated with a protein-free extract of pituitary free from gonadotropic, growth and thyrotropic hormones. Reticulocytosis developed during the injection. The authors favor the theory of a hemopoietic hormone.

Polonovski and Briskas²³³ feel that in rats and dogs cobalt polycythemia is probably the result of an increase in the total blood volume resulting from the toxic action of cobalt, rather than the new formation of red blood cells.

230 Palitz, L. L. Splenic Volume and the Polycythemia of Artificial Fever in Intact, Unanesthetized Dogs, *Am J Physiol* **125** 607, 1939.

231 Gibson, J. G. Jr., Harris, A. W., and Swigert, V. W. Clinical Studies of the Blood Volume. VIII. The Blood Volume in Secondary Anemia and Polycythemia Vera, *J Clin Investigation* **18** 621, 1939.

232 Flaks, J., Himmel, I., and Zotnik, A. La polyglobulie provoquee par les extraits de lobe anterieur d'hypophyse prouve l'existence d'une hormone hemopoietique, *Presse med* **46** 1506, 1938.

233 Polonovski, M., and Briskas, S. Contribution a l'etude de l'action hemopoietique du cobalt au cours de l'anemie provoquee chez le jeune rat carence, *Compt rend Soc de biol* **130** 1588, 1939. Le role des sels de cobalt dans l'anemie provoquee chez le chien, *ibid* **130** 1590, 1939.

Kleinberg, Gordon and Charipper,²³⁴ however, found that cobalt salts injected into rabbits subjected to repeated bleedings or treated with benzene promote rapid recovery from anemia by stimulation of the formation of erythrogenic precursors in the bone marrow

Okranetz²³⁵ has described in detail the treatment of polycythemia by "total body irradiation." A symptomatic remission of fifteen months' duration was produced by giving 235 r (measured in air) to the anterior surface of the body and 210 r posteriorly, in individual doses of 25 r over a period of thirty-five days. With the subsequent relapse, the symptoms and the polyglobulia returned, but four treatments (25 r each) were sufficient to produce a remission for another year. The author feels that small doses given by total body irradiation, with protection of the eyes, spleen and, in this case, ovaries, is preferable to larger doses over single bones.

Anderson, Geill and Samuelson²³⁶ treated 2 patients with polycythemia by roentgen therapy over the pylorus. The position was located fluoroscopically. Four series of treatments were given at monthly intervals. Hematologic improvement was noted. Hitzenger in 1931 used a similar type of therapy, with production of a temporary remission. The underlying theory was based on the hope of destroying or inhibiting the production of the intrinsic factor of Castle, thus delaying production of red blood cells.

Kaplan²³⁷ finds that polycythemia vera is most satisfactorily controlled by high voltage roentgen therapy over the sternum and ribs. He recommends 200 kilovolts potential with filtration of 0.5 mm of copper plus 1 mm of aluminum at a distance of 40 to 50 cm. Individual doses of 150 to 200 r (measured in air) are repeated every third day. Remissions lasting as long as forty weeks have been produced. When intensive irradiation is directed to the spleen, there is a rise in the red blood cell count.

The treatment of polycythemia associated with pulmonary hypertension (Ayerza's disease), complicated by arterial hypertension and marked obesity, should aim to reduce the viscosity of the blood and prevent thrombosis, according to the experience of Olsen and Willius²³⁸

234 Kleinberg, W., Gordon, A. S., and Charipper, M. A. Effect of Cobalt on Erythropoiesis in Anemic Rabbits, *Proc Soc Exper Biol & Med* **42** 119, 1939

235 Okranetz, C. L. Total Body Irradiation in Polycythemia Vera, *M Woman's J* **46** 203, 1939

236 Anderson, F., Geill, T., and Samuelson, E. Polycythemia Treated with Roentgen Irradiation of Pylorus Organ, *Acta med Scandinav* **97** 547, 1938

237 Kaplan, I. Treatment of Polycythemia with Roentgen Ray, *Radiology* **33** 166-169, 1939

238 Olsen, A. M., and Willius, F. A. Cardiac Clinics. LVI. Clinic on Cardiac Failure Resulting from Pulmonary Hypertension (Ayerza's Disease) Complicated by Arterial Hypertension and Marked Obesity, *Proc Staff Meet, Mayo Clin* **14** 89, 1939

Venesection is the method of choice. Some degree of activity should be allowed to the patient, and unnecessary injury of the veins is to be avoided to prevent local thrombosis.

The treatment advocated by Herzog and Kleiner²³⁹ consists in limiting the animal protein to 0.7 Gm a day. There was a definite decrease in the number of red blood cells, in some cases at the end of one week and in others at longer intervals. Hypertension was lowered and splenomegaly decreased. Of 19 cases, the treatment was successful in 17. A less strict diet (1 pint of milk, 100 Gm of cheese, 200 Gm of fish daily, 3 eggs or 150 Gm of veal twice weekly) was prescribed when the improvement in the blood set in.

PURPURA

Of the many bleeding disorders, purpura haemorrhagica is one of the least understood. This is undoubtedly due to the multiple etiologic factors and to the confusion created by the various classifications. Forkner,²⁴⁰ in an excellent review of the hemorrhagic diseases, states that they should be classified according to their clinical picture rather than according to the pathologic condition present or the physiologic mechanisms involved. In spite of this viewpoint, he includes the latter in his excellent tables. Six cases of essential thrombopenic purpura have been studied by Heinild.²⁴¹ According to this investigator the outstanding characteristics of the disease are the unknown cause, the spontaneous hemorrhages, the decrease or absence of platelets, the prolonged bleeding time and the poor clot retraction. The course may be acute or chronic, and the disease usually occurs in women. In addition to the essential type of thrombopenic purpura, the author also described symptomatic, allergic and hypersplenic purpura.

Elliott²⁴² classifies purpuras as primary or secondary. The latter may have such etiologic factors as infections, poisons, nutritional deficiencies and disturbances of the reticuloendothelial system and bone marrow. The platelets may or may not be reduced in number. The cause of the primary type of purpura is not known. Elliott, in addition

239 Herzog, F, and Kleiner, G. Ergebnis der Diätbehandlung in neunzehn Fällen von Polyzythämie, *Deutsche med Wchnschr* **65** 719, 1939, *Therapy of Polycythemia. Results in Nineteen Cases*, *Orvosi hetil* **83** 357, 1939.

240 Forkner, C E. An Attempt to Consolidate and to Clarify Present Views Concerning the Anemias and the Hemorrhagic Disorders, *Proc A Life Insur M Dir America* (1938) **25** 258, 1939.

241 Heinild, S. Observations on Essential Thrombopenia (Morbus Maculosus Werlhofii), *Acta med Scandinav* **98** 385, 1939.

242 Elliott, R H E. Diagnostic and Therapeutic Considerations in the Management of Idiopathic Thrombocytopenic Purpura, *Bull New York Acad Med* **15** 197, 1939.

to the characteristics of the disorder mentioned by the previous writers, states that the course in adults and children varies. With the younger patients spontaneous recoveries are common. This opinion is shared by Rosenthal,²⁴³ who has adequately reviewed the etiology, course and treatment of the disease.

So-called secondary purpura due to various drugs has been reported by many authors. McGovern and Wright²⁴⁴ and Huber²⁴⁵ describe cases in which the offending substance was sedormid. Sexton²⁴⁶ and Wyatt²⁴⁷ noted the occurrence of bleeding following the use of arsphenamine.

The role of the spleen in the production of thrombopenic purpura was investigated by Major and Weber²⁴⁸ and by Pohle and Meyer.²⁴⁹ These authors attempted to reproduce the disease in rabbits by injecting extracts prepared from spleens removed from patients with thrombopenic purpura. All attempts met with failure. Major and Weber state that their failure to substantiate the previous reports that a platelet-reducing substance is present may be due to differences in their extracts. Pohle and Meyer offer no explanation for their failure to reproduce the disease but state definitely that a platelet-reducing substance does not exist in the spleens of patients with essential purpura.

The pathologic anatomy of experimental thrombopenic purpura in the dog was studied by Toncantins and Stewart.²⁵⁰ Antiplatelet serum was prepared from washed platelets of dogs and injected into rabbits. The experiments included several groups or types: (1) fatal, (2) serial short intravenous, (3) multiple doses and (4) control. In all instances generalized hemorrhages were produced. The purpura produced by the intraperitoneal route, according to the authors, simulated true purpura as seen in man. The course was described as follows in the acute stage

243 Rosenthal, N. The Course and Treatment of Thrombopenic Purpura, *J A M A* **112** 101 (Jan 14) 1939

244 McGovern, T, and Wright, I. Purpura Haemorrhagica Following Use of Sedormid, *J A M A* **112** 1687 (April 29) 1939

245 Huber, H. H. A Case of Purpura Haemorrhagica Resulting from Sedormid, *J A M A* **113** 674 (Aug 19) 1939

246 Sexton, G. B. Caution in Arsphenamine Therapy, *Canad M A J* **40** 378, 1939

247 Wyatt, W. A Case of Peripheral Neuritis Due to Neoarsphenamine, and Purpura Hemorrhagica Due to Bismuth Arsphenamine Sulphonate, *M Rec* **149** 349, 1939

248 Major, R. H., and Weber, C. J. Is There a Platelet Reducing Substance in the Spleen of Thrombocytopenic Purpura? *J Lab & Clin Med* **25** 10, 1939

249 Pohle, F. J., and Meyer, O. O. Inability to Demonstrate a Platelet Reducing Substance in an Acetone Extract of the Spleen from Patients with Idiopathic Thrombocytopenic Purpura, *J Clin Investigation* **18** 537, 1939

250 Toncantins, L. M., and Stewart, H. L. Pathological Anatomy of Experimental Thrombopenic Purpura in the Dog, *Am J Path* **15** 1, 1939

(first to fifth day), thrombopenia, a prolonged bleeding time, hemorrhage, edema, and deposition of pigment were the outstanding characteristics, the intermediate stage (fifth to tenth day) was identified by the occurrence of multiple vascular thrombi, principally in the spleen, and a short bleeding time, and the third, or reactive, stage appeared after the tenth day. The platelet count was normal or increased, follicular hemorrhages were present in the spleen and hyperplastic changes were noted in the bone marrow, the spleen, the lymph nodes, the thymus and Peyer's patches. In summary, these investigators point out that hemorrhages are seen usually in organs with changing pressures and are rare in more stable organs. Trauma must also be considered as an important factor.

Multiple cases of atypical purpura have been reported. Schindler²⁵¹ describes chronic localized gastric purpura and believes that it is a new disease. He also stresses its relation to chronic gastroduodenal ulcer and suggests the possibility that it may be the initial lesion in the development of the ulcer. Leukothrombopenia associated with increased capillary permeability is described by Madison and Squier²⁵². These authors are of the opinion that this is a definite clinical syndrome. The characteristics of renal purpura and its differences from the renal hemorrhages associated with thrombopenic purpura are reported by Dukes²⁵³. Levinson²⁵⁴ reviews the history of the Waterhouse-Fridericksen syndrome and reports a case studied by himself. The disease is characterized by the sudden onset of malaise, vomiting, diarrhea, fever, rapid pulse, cyanosis, purpura, lethargy, coma and death. The cause is not definitely known, though bacteremia or toxemia is considered the most likely. Pathologic studies reveal hemorrhages in the adrenal glands in addition to generalized purpura.

The treatment of purpura is dependent on the cause, which must be established. It must also be kept in mind that relapses and remissions are common and that the therapeutic results obtained may be dependent to a certain extent on this characteristic of the disease. As is suggested by Limarzi and Schleicher,²⁵⁵ studies of the bone marrow are of considerable aid in identifying true thrombopenic purpura and in determining when splenectomy is indicated. Heimold is of the opinion that

251 Schindler, R. Chronic Localized Gastric Purpura, *Am J Digest Dis* **5** 796, 1939.

252 Madison, F. W., and Squier, T. L. Leukothrombopenia with Increased Capillary Permeability, *J A M A* **112** 879 (March 4) 1939.

253 Dukes, C. E. Renal Purpura, *Proc Roy Soc Med* **32** 1322, 1939.

254 Levinson, S. A. The Waterhouse-Fridericksen Syndrome, *J Pediat* **14** 506, 1939.

255 Limarzi, L. R., and Schleicher, E. M. Bone Marrow in the Active Phase of Essential Thrombopenic Purpura, *J A M A* **112** 899 (March 4) 1939.

splenectomy is of considerable value for purpura but recommends a trial of conservative therapy first. Elliott compared the results following splenectomy in cases of true thrombopenia and in cases of atypical purpura. In the first group, of 21 cases, 13 patients were cured, 5 were definitely improved, 2 were improved but not free from symptoms, and 1 died. In the second group, of 11 cases, there were 4 cures and 5 deaths, and 2 patients showed no improvement.

Bernstein and his co-workers²⁵⁶ report the unusual occurrence of idiopathic thrombopenia in pregnancy and the neonatal period. Splenectomy was successfully performed during the sixth month of pregnancy. Menorrhagia as the outstanding feature of purpura is noted by Jennings and Castleden²⁵⁷ and by Israel and Mendell²⁵⁸. Splenectomy was of little benefit to the patient of Jennings and Castleden but produced a cure in the patient of Israel and Mendell. Vaughan and Wright²⁵⁹ observed 6 patients for at least ten years after splenectomy. They concluded that the results of this type of therapy in properly selected cases are not only good but permanent.

This opinion is shared by Rosenthal,²⁴³ who, in addition, has summarized the results obtained with various other types of therapy. Ascorbic acid, liver extract, parathyroid extract and roentgen irradiation are of no value. Sesame oil is useless, a conclusion substantiated by Olson.²⁶⁰ Snake venom is recommended for secondary purpura. Transfusions are of temporary help. Ligation of the splenic artery fails to give any relief.

HEMOPHILIA

As with many other diseases, the cause of hemophilia has not been identified. Howell²⁶¹ states that there is a deficiency in the plasma of some substance as yet unknown. For brevity he uses the term "thromboplastin" and distinguishes two types, plasma thromboplastin and tissue thromboplastin. Plasma thromboplastin can be obtained from citrated blood by saturation with carbon dioxide or by addition of acid. This

256 Bernstein, P., Newman, A. B., and Hitzig, W. M. The Problem of Idiopathic Purpura Hemorrhagica in Pregnancy and the Neonatal Period, *Am J Obst & Gynec* **38** 323, 1939.

257 Jennings, G. H., and Castleden, L. I. M. Thrombocytopenic Purpura, *Lancet* **1** 931, 1939.

258 Israel, S. L., and Mendell, T. H. Severe Menorrhagia as the Only Symptom of Essential Thrombocytopenic Purpura Cured by Splenectomy, *Am J Obst & Gynec* **38** 339, 1939.

259 Vaughan, S. L., and Wright, T. Purpura Haemorrhagica, with Special Reference to Permanence of Remission Following Splenectomy, *J A M A* **112** 2120 (May 27) 1939.

260 Olson, K. B. The Effect of Sesame Oil ("T-Factor") on the Platelet Count, *Proc Soc Exper Biol & Med* **41** 643, 1939.

261 Howell, W. H. Hemophilia, *Bull New York Acad Med* **15** 3, 1939.

substance is associated with all proteins in the blood. In hemophilic blood it is present in smaller amounts than normal. This fact was established by adding thromboplastin extracts from normal and hemophilic blood to hemophilic blood and observing the differences in clotting time. Similar results were noted with tissue thromboplastin. In the author's opinion, platelets are the source of plasma thromboplastin, if the plasma is normal hemophilic platelets will react normally, but otherwise they appear to be more stable, with a resulting prolongation of the clotting time.

The coagulation defect associated with hemophilia has also been investigated by Lozner and his co-workers²⁶². These investigators prepared a clot-promoting substance from normal human plasma free from fibrinogen and prothrombin. When this material was added to hemophilic blood, clotting proceeded at a rate proportional to the amount of substance added. When the clot-promoting substance was injected intravenously, the coagulation time readily decreased. Multiple injections at six hour intervals further decreased the clotting time, there was no evidence of any refractory period.

Ferguson²⁶³ has also studied the mechanism of clotting in hemophiliacs. He believes that there is a deficiency in the amount of "thromboplastic enzyme" in hemophilic blood and that because of the lack of this substance there is a delay in coagulation. Bendien and van Creveld²⁶⁴ prepared a globulin-like protein substance and investigated its coagulation-promoting activity, especially in relation to hemophilia. This substance was ineffective when administered orally or intramuscularly but readily decreased the clotting time when injected intravenously. Similar results were obtained with a preparation from placenta, though to a lesser degree. It is the author's opinion that this coagulation-promoting substance is related to prothrombin.

Platelet studies of normal men, of women (menstruating and nonmenstruating) and of persons with bleeding disorders were made by Lee and Erickson²⁶⁵. From their observations they conclude that

262 Lozner, E. L., Kark, R., and Taylor, F. H. L. The Coagulation Defect in Hemophilia. The Clot Promoting Activity in Hemophilia of Berkefelded Normal Human Plasma Free from Fibrinogen and Prothrombin, *J. Clin. Investigation* **18** 603, 1939.

263 Ferguson, J. H. The Clotting of Hemophilic Plasma by Thromboplastic Enzyme, *Am. J. Physiol.* **126** 669, 1939.

264 Bendien, W. M., and van Creveld, S. On Some Factors of Blood Coagulation, Especially with Regard to the Problem of Hemophilia, *Acta med. Scandinav.* **99** 12, 1939.

265 Lee, P., and Erickson, B. N. Platelet Studies in Normal Men and Women (Menstruating and Nonmenstruating) and Subjects with Bleeding Disorders, *J. Lab. & Clin. Med.* **24** 821, 1939.

there is a similarity in the abnormal clotting of the blood of menstruating women and that of hemophiliacs

Owing to the bleeding tendency, complications often arise in cases of hemophilia. Paltrimeri²⁶⁶ and Newcomer²⁶⁷ emphasize the frequency of hemorrhage into joints with contractures. The dangers to be encountered in hemophilia when operations are necessary are stressed by Vance²⁶⁸. His conclusions are most important. Hemophiliacs should not be subjected to an operation unless the danger to life is increased as the result of deprivation of the operation. If surgical intervention is contemplated, the patient should be adequately prepared with transfusions. Howell²⁶¹ also states that the only reliable treatment for hemophilia is transfusion.

BLOOD CLOTTING

A most complete résumé on vitamin K has been published by Snell and Butt²⁶⁹. These authors point out the difficulties associated with the problem related to the defining of a unit of the vitamin. Ansbacher²⁷⁰ defines a unit of vitamin K as the minimum amount necessary to render the clotting time of the blood of the vitamin K-deficient chick weighing 70 to 100 Gm normal within six hours after administration. This unit equals 20 Dam units. Thayer and his co-workers²⁷¹ assayed vitamins K₁ and K₂ and defined a unit as that quantity of vitamin K which produces a clotting time of ten minutes or less in 50 per cent of a group of 10 or more chicks which have been fed for the fourteen days immediately following receipt from the hatcher on a diet practically devoid of vitamin K. By these standards, vitamin K₁ contains approximately 1,000 units per milligram and vitamin K₂ about 600 units per milligram. Dam and Glavind and Almquist and his associates have also established units of activity which are at considerable variance with the units just defined. It is readily apparent that for the present no unit can arbitrarily be established which would be suitable to all investigators.

The isolation and purification of vitamin K may soon be a reality. Almquist and Klose²⁷² have prepared a choleic acid derivative, which

266 Paltrimeri, M. Osservazioni di retrazione ischemiche di Volkmann in emofiliaci, *Bull d sc med*, Bologna **111** 203, 1939.

267 Newcomer, N. B. The Joint Changes in Hemophilia, *Radiology* **32** 573, 1939.

268 Vance, C. A. Surgery in Hemophilia, *Ann Surg* **109** 872, 1939.

269 Snell, A. M., and Butt, H. R. Supplementary Report on Vitamin K, *J A M A* **113** 2056 (Dec 2) 1939.

270 Ansbacher, S. A Quantitative Biological Assay of Vitamin K, *J Nutrition* **17** 303, 1939.

271 Thayer, S. A., McKee, R. W., Binkley, S. B., MacCorquodale, D. W., and Doisy, E. A. Assay of Vitamin K Concentrates, *Proc Soc Exper Biol & Med* **40** 478, 1939, The Assay of Vitamins K₁ and K₂, *ibid* **41** 194, 1939.

272 Almquist, H. J., and Klose, A. A. The Isolation of Vitamin K as a Choleic Acid, *J Am Chem Soc* **61** 745, 1939.

is a yellow crystalline substance with a melting point of 186 C. The K vitamin can be separated from this substance as a viscous, slightly pigmented oil. The effect of this substance on prothrombin levels when fed orally to rats with bile fistulas was investigated by Cohn and Schmidt²⁷³. Although their results were poor, it is their opinion that the doses of the material were too small. By a process of molecular distillation and chromatographic methods, Dam and his co-workers²⁷⁴ prepared a substance which they believed was the pure vitamin K. It contains about 20,000,000 Dam units per gram by biologic assay. Chemically, it appears as a clear yellowish oil containing carbon, hydrogen and oxygen and is free of nitrogen.

McKee and his collaborators²⁷⁵ isolated vitamins K₁ and K₂ from alfalfa and putrefied fish meal respectively. Subsequent work²⁷⁶ suggested that the vitamins have a quinoid structure. Almquist and Klose²⁷⁶ noted that phthiocol has physical and chemical properties similar to pure vitamin K. Fernholz and Ansbacher²⁷⁷ demonstrated that synthetic phthiocol has antihemorrhagic properties and noted its powerful curative effects in chicks deficient in vitamin K. Phthiocol was first isolated (1933) and synthesized (1934) by Anderson and his co-workers. The antihemorrhagic activity of phthiocol is considered by Almquist and Klose²⁷⁸ to be somewhere between that of methylnaphthoquinone and hydroxynaphthoquinone. The latter group appears to reduce the activity, while the former is functionally important. Ansbacher and Fernholz²⁷⁹ agree with the opinion of Almquist and Klose that phthiocol is of less potency than is the more complex form of vitamin K in alfalfa.

273 Cohn, E. J., and Schmidt, C. L. A. Effect of Choleic Acid of Vitamin K on Prothrombin Levels of Bile Fistula Rats, *Proc Soc Exper Biol & Med* **41** 443, 1939.

274 Dam, H., Geiger, A., Glavind, J., Karrer, P., Karrer, W., Rothschild, E., and Solomon, H. Isolierung des Vitamins K in hochgereinigter Form, *Helvet chim acta* **22** 310, 1939.

275 McKee, R. W., Binkley, S. B., MacCorquodale, D. W., Thayer, S. A. and Doisy, E. A. The Isolation of Vitamins K₁ and K₂, *J Am Chem Soc* **61** 1295, 1939. Binkley, S. B., MacCorquodale, D. W., Cheney, L. C., Thayer, S. A., McKee, R. W., and Doisy, E. A. Derivatives of Vitamins K₁ and K₂, *ibid* **61** 1612, 1939.

276 Almquist, H. J., and Klose, A. A. The Antihemorrhagic Activity of Pure Synthetic Phthiocol, *J Am Chem Soc* **61** 1611, 1939.

277 Fernholz, E., and Ansbacher, S. Vitamin K Activity of Synthetic Phthiocol, *Science* **90** 215, 1939.

278 Almquist, H. J., and Klose, A. A. The Antihemorrhagic Activity of Certain Naphthoquinones, *J Am Chem Soc* **61** 1923, 1939.

279 Ansbacher, S., and Fernholz, E. Simple Compounds with Vitamin K Activity, *J Am Chem Soc* **61** 1924, 1939.

The structure of the antihemorrhagic vitamin has been the subject of considerable investigation. Thayer and his colleagues,²⁸⁰ as well as MacCorquodale and his associates,²⁸¹ found that 2-methyl-1, 4-naphthoquinone is the most effective substance, but its activity compared to the natural vitamins K₁ and K₂ is negligible. The K₁ molecule is believed to be 2-ethyl-3-phytyl-1, 4-naphthoquinone. It is suggested by Fieser and his collaborators²⁸² that the structure of vitamin K₁ is 2, 6 (2) - dimethyl-3-phytyl-1, 4-naphthoquinone and that the structure of vitamin K₂ is 2, 3-diforanesyl-1, 4-naphthoquinone. By means of synthesis, Binkley and his associates²⁸³ demonstrated conclusively that vitamin K₁ is 2-methyl-3-phytyl-1, 4-naphthoquinone. Fieser, Campbell, Fry and Gates²⁸⁴ describe the synthesis of vitamin K₁ and confirm its chemical structure. Since this synthetic compound has an activity equivalent to that of pure vitamin K₁, it is suggested by Thayer and his co-workers²⁸⁵ that it be adopted as a basic standard for the assay of vitamin K. With the exception of its instability when exposed to light,²⁸⁶ it has all the necessary requisites of a product suitable for standardization.

The methods of determining prothrombin time present a problem which at present does not appear too important, since the nature of prothrombin is not known. Ziffren and his associates²⁸⁷ describe a "bedside" technic for determining the clotting time of an unknown specimen of blood and comparing the results with those obtained with

280 Thayer, S. A., Cheney, L. C., Binkley, S. B., MacCorquodale, D. W. and Doisy, E. A. Vitamin K Activity of Some Quinones, *J. Am. Chem. Soc.* **61** 1932, 1939.

281 MacCorquodale, D. W., Binkley, S. B., Thayer, S. A., and Doisy, E. A. On the Constitution of Vitamin K₁, *J. Am. Chem. Soc.* **61** 1928, 1939.

282 Fieser, L. F., Bowen, D. M., Campbell, W. P., Fieser, M., Fry, E. M., Jones, R. N., Riegel, B., Schweitzer, C. E., and Smith, P. G. Quinones Having Vitamin K Activity, *J. Am. Chem. Soc.* **61** 1925, 1939.

283 Binkley, S. B., MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A. The Isolation of Vitamin K₁, *J. Biol. Chem.* **130** 219, 1939.

284 Fieser, L. F., Campbell, W. P., Fry, E. M., and Gates, M. D., Jr. Synthetic Approach to Vitamin K₁, *J. Am. Chem. Soc.* **61** 2559, 1939.

285 Thayer, S. A., Binkley, S. B., MacCorquodale, D. W., Doisy, E. A., Emmett, A. D., Brown, R. A., and Bird, O. D. Vitamin K Potencies of Synthetic Compounds, *J. Am. Chem. Soc.* **61** 2563, 1939.

286 MacCorquodale, D. W., Binkley, S. B., McKee, R. W., Thayer, S. A., and Doisy, E. A. Inactivation of Vitamin K by Light, *Proc. Soc. Exper. Biol. & Med.* **40** 482, 1939.

287 Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P. Control of Vitamin K Therapy. Compensatory Mechanisms at Low Prothrombin Levels, *Proc. Soc. Exper. Biol. & Med.* **40** 595, 1939, *Clinical and Experimental Studies on Vitamin K*, *J. A. M. A.* **113** 380 (July 29) 1939.

normal blood Thromboplastin is added to each specimen The unknown is expressed in percentage of the normal Pohle and Stewart²⁸⁸ studied the Quick method for quantitative determination of prothrombin and criticized it on the basis that there are too many variables which influence the results In answer to this criticism Quick²⁸⁹ pointed out that by standardizing the technic the variables can be discounted In justification of the various tests recommended, it should be kept in mind that, whichever method is used for determining the prothrombin deficiency, the results are dependent on the experience of the physician concerned Boyce and McFetridge²⁹⁰ have devised a serum volume test for determination of the bleeding tendency in cases of jaundice Three cubic centimeters of blood is removed from the patient and permitted to stand at room temperature for four hours The serum volume divided by 1.5 cc gives an index of 1 or more, which is considered normal Indexes less than 1 are indicative of hemorrhage This test proved to be satisfactory in 21 cases studied

Several conditions in which prothrombin deficiency may exist and can be corrected by administration of vitamin K have been reported Waddell and Guerry²⁹¹ noted that the prothrombin level in newborn infants is often low and that there is considerable variation in individual infants from day to day The newborn with a bleeding tendency and those with low prothrombin levels readily responded to vitamin K therapy Quick and Grossman²⁹² noted that the prothrombin concentration was high for the first six hours after birth, rapidly decreased for the next twenty-four to forty-eight hours and then gradually increased They suggest that an important factor in the increase of prothrombin is synthesis of vitamin K by bacteria in the gastrointestinal tract Owen and his co-workers²⁹³ noted a continual decrease in the prothrombin

288 Pohle, F. J., and Stewart, J. K. A Study of the Quick Method for the Quantitative Determination of Prothrombin, with Suggested Modifications, *Am J M Sc* **198** 622, 1939

289 Quick, A. J. Calcium Factor in Quantitative Determination of Prothrombin, *Proc Soc Exper Biol & Med* **40** 206, 1939

290 Boyce, F. F., and McFetridge, E. M. The Serum Volume Test for the Hemorrhagic Diathesis in Jaundice. Further Observations, *New Orleans M & S J* **91** 357, 1939

291 Waddell, W. W., Jr., and Guerry, D., III. Effect of Vitamin K on the Clotting Time of the Prothrombin and the Blood, *J A M A* **112** 2259 (June 3) 1939

292 Quick, A. J., and Grossman, A. M. Prothrombin Concentration in Newborn, *Proc Soc Exper Biol & Med* **41** 227, 1939, Concentration of Prothrombin in Blood of Babies (Three to Seven Days Old), *ibid* **40** 647, 1939

293 Owen, C. A., Hoffman, G. R., Ziffren, S. E., and Smith, H. P. Blood Coagulation During Infancy, *Proc Soc Exper Biol & Med* **41** 181, 1939

concentration of the blood of newborn infants for six days. They state that their findings, which are opposite to those of Quick, can be explained by the fact that their method estimates prothrombin only, whereas Quick's method does not take into account the conversion time of prothrombin, which is a most important compensating factor. Hellman and Shettles²⁹⁴ recommend on the basis of their investigations that prothrombin deficiency in premature infants can be prevented by feeding vitamin K to the mother or corrected by administering vitamin K to the infant. Shettles, Delfs and Hellman²⁹⁵ noted that after administration of vitamin K to the mother the prothrombin level of the infant is about three times the normal. Waddell and his collaborators²⁹⁶ and Nygaard²⁹⁷ suggest the use of vitamin K as a preventive and curative measure for hemorrhagic disease of the newborn.

Snell and Butt,²⁹⁹ in their supplementary report on vitamin K, discuss the possibility that prothrombin deficiency may occur as a result of an inadequate intake of this vitamin. This clinical observation is readily substantiated by the experimental work of Greaves,²⁹⁸ Murphy²⁹⁹ and Almquist and Klose,³⁰⁰ who produced hypotherbinemia in animals after administration of a diet deficient in vitamin K.

Prothrombin deficiency may result from various intestinal disorders, as has been demonstrated by Clark, Dixon, Butt and Snell.³⁰¹ Similar observations are noted by Olson,³⁰² Smith, Ziffren, Owen, Hoffman

294 Hellman, L. M., and Shettles, L. B. Factors Influencing Plasma Prothrombin in the Newborn Infant. I. Prematurity and Vitamin K, *Bull. Johns Hopkins Hosp.* **65** 138, 1939.

295 Shettles, L. B., Delfs, E., and Hellman, L. M. Factors Influencing Plasma Prothrombin in the Newborn Infant. II. Antepartum and Neonatal Ingestion of Vitamin K Concentrate, *Bull. Johns Hopkins Hosp.* **65** 419, 1939.

296 Waddell, W. W., Jr., Guerry, D., III, Bray, W. E., and Kelley, O. R. Possible Effects of Vitamin K on Prothrombin and Clotting Time in Newly-Born Infants, *Proc. Soc. Exper. Biol. & Med.* **40** 432, 1939.

297 Nygaard, K. K. Prophylactic and Curative Effect of Vitamin K in Hemorrhagic Disease of the Newborn (Hypotherbinemia Hemorrhagica Neonatorum), *Acta obst. et gynec. Scandinav.* **19** 361, 1939.

298 Greaves, J. D. Studies on the Vitamin K Requirement of Rats, *Am. J. Physiol.* **125** 429, 1939.

299 Murphy, R. Possible Avitaminosis K Produced in Mice by Dietary Means, *Science* **89** 203, 1939.

300 Almquist, H. J., and Klose, A. A. Determination of the Anti-Haemorrhagic Vitamin, *Biochem. J.* **33** 1055, 1939.

301 Clark, R. L., Jr., Dixon, C. F., Butt, H. R., and Snell, A. M. Deficiency of Prothrombin Associated with Various Intestinal Disorders. Its Treatment with the Antihemorrhagic Vitamin (Vitamin K), *Proc. Staff Meet., Mayo Clin.* **14** 407, 1939.

302 Olson, P. F. The Prothrombin Test and the Vitamin K Treatment for the Bleeding Tendency in the Jaundiced Patient, *J. Iowa M. Soc.* **29** 103, 1939.

and Flynn,³⁰³ Olson and Menzel,³⁰⁴ Butt, Snell and Osterberg,³⁰⁵ Stewart,³⁰⁶ Stewart and Rourke,³⁰⁷ and Townsend and Mills³⁰⁸

It has been suggested that the liver synthesizes prothrombin and that a hemorrhagic tendency may be associated with severe hepatic damage. Clinically, this is reported by Scanlon and his associates³⁰⁹. A similar condition has been produced in hepatectomized dogs by Warren and Rhoads³¹⁰ in carefully controlled experiments. Warner³¹¹ also demonstrated the occurrence of hypoprothrombinemia in rats after removal of the liver. A close correlation between prothrombin deficiency and hippuric acid excretion in persons with disease of the liver was observed by Wilson³¹². He suggests that hypoprothrombinemia may be indicative of severe hepatic damage. Wilson and Doan³¹³ noted a hemorrhagic tendency in rabbits following artificially produced fever and concluded that the bleeding was due not only to decreased platelets but to decreased prothrombin and fibrinogen resulting from severe hepatic necrosis.

Satisfactory treatment for prothrombin deficiency may be accomplished by oral administration of vitamin K. Butt, Snell and Oster-

303 Smith, H. P., Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Flynn, J. E. The Jaundiced Bleeder. Control of Hemorrhage Through Vitamin K, *J. Iowa M. Soc.* **29** 377, 1939.

304 Olson, K. B., and Menzel, H. Bleeding Tendency in Obstructive Jaundice and Its Correction by Means of Vitamin K, *Surgery* **6** 206, 1939.

305 Butt, H. R., Snell, A. M., and Osterberg, A. E. The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, *J. A. M. A.* **113** 383 (July 29) 1939.

306 Stewart, J. D. Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, *Ann. Surg.* **109** 588, 1939.

307 Stewart, J. D., and Rourke, G. M. Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K, *J. A. M. A.* **113** 2223 (Dec. 16) 1939.

308 Townsend, S. R., and Mills, E. S. Use of Vitamin K and Bile Salts in Prevention and Control of Hemorrhagic Diathesis in Obstructive Jaundice, *Canad. M. A. J.* **41** 111, 1939.

309 Scanlon, G. H., Brinkhous, K. M., Warner, E. D., Smith, H. P., and Flynn, J. E. Plasma Prothrombin and the Bleeding Tendency, with Special Reference to Jaundiced Patients and Vitamin K Therapy, *J. A. M. A.* **112** 1898 (May 13) 1939.

310 Warren, R., and Rhoads, J. E. Hepatic Origin of Plasma-Prothrombin. Observations After Total Hepatectomy in the Dog, *Am. J. M. Sc.* **198** 193, 1939.

311 Warner, E. D. Plasma Prothrombin. Effect of Partial Hepatectomy, *J. Exper. Med.* **68** 831, 1938.

312 Wilson, S. J. Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, *Proc. Soc. Exper. Biol. & Med.* **41** 559, 1939.

313 Wilson, S. J., and Doan, C. A. Pathogenesis of Hemorrhage in Artificially Produced Fever, *Proc. Soc. Exper. Biol. & Med.* **41** 115, 1939.

berg³¹⁴ report successful results with intravenous administration of phthiocol Cheney³¹⁵ treated chicks with a hemorrhagic tendency by intramuscular injections of vitamin K and concluded that it is a satisfactory and safe procedure Tage-Hansen³¹⁶ compared the oral vitamin K therapy with parenteral methods In his opinion, intravenous treatment should be given in cases of urgent need, intramuscular treatment has the advantage of prolonged effect but is in reality the poorest type of therapy Lord and Pastore³¹⁷ measured the prothrombin content of "bank" blood and consider it satisfactory for transfusion purposes if stored for less than six to seven days The prothrombin content of the blood of dogs after transfusions was studied by Lord, Andrus and Moore³¹⁸ A definite increase in prothrombin was noted The authors conclude that the changes in the prothrombin of the recipient are dependent on the prothrombin content of the plasma of the donor and may be calculated on the basis of addition

In addition to the vitamin K studies, many interesting observations have been made relative to blood clotting The characteristics of blood clot formation are described by McKhann and Edsall³¹⁹ Thiberge³²⁰ noted that the blood platelets were reduced in number during allergic attacks and increased during convalescence If it can be assumed that allergic reactions are associated with increased histamine, the observations of Thiberge are opposite to those of Zon, Ceder and Crigler,³²¹ who conclude that the histamine content of the blood is dependent on the number of platelets present Anrep and his associates³²² studied the effect of clotting on the distribution of histamine in the blood Approxi-

314 Butt, H R , Snell, A M , and Osterberg, A E Phthiocol Its Therapeutic Effect in the Treatment of Hypoprothrombinemia Associated with Jaundice, a Preliminary Report, Proc Staff Meet, Mayo Clin **14** 497, 1939

315 Cheney, G The Intramuscular Injection of Vitamin K, J Lab & Clin Med **24** 919, 1939

316 Tage-Hansen, E Summary of Some Chemical Studies on Vitamin K, J A M A **113** 1875 (Nov 18) 1939

317 Lord, J. R, Jr, and Pastore, J B Plasma Prothrombin Content of Bank Blood, J A M A **113** 2231 (Dec 16) 1939

318 Lord, J W, Jr , Andrus, W DeW, and Moore, R A Quantitative Study of Effect of Transfusion of Blood on Plasma Prothrombin, Proc Soc Exper Biol & Med **41** 98, 1939

319 McKhann, C F, and Edsall, G Characteristics of Blood Clot Formation, Pennsylvania M J **42** 731, 1939

320 Thiberge, N F The Thrombocyte in Allergy, New Orleans M & S J **91** 372, 1939

321 Zon, L , Ceder, E T, and Crigler, C W The Presence of Histamine in the Platelets of the Rabbit, Pub Health Rep **54** 1978, 1939

322 Anrep, G V , Barsoum, G S , Talaat, M, and Weininger, E Effect of Clotting and of Addition of Histamine on Its Distribution in Blood, J Physiol. **96** 130, 1939

mately 50 to 60 per cent of the histamine content of the blood is in the white blood cells. Clotting does not release histamine to the serum.

Volker³²³ observed the effect of saliva on coagulation of the blood. Clotting time was readily reduced by the addition of saliva. Neither boiling nor Berkefeld filtration altered the effect of saliva. Putnam and Hoefer³²⁴ performed *in vitro* and *in vivo* experiments with cysteine hydrochloride and noted its anticoagulant effects. Similar effects were noted with heparin by Astrup³²⁵ and by Lucia and Aggeler³²⁶. Milliken³²⁷ and Schumann³²⁸ observed a decreased bleeding time with cessation of bleeding when suitable amounts of oxalic acid were given parenterally to patients.

Copley³²⁹ studied the specificity of thrombin action and points out that it is a catalyst for fibrinogen. Meitz, Seegers and Smith³³⁰ experimented with various amounts of purified thromboplastin, prothrombin and calcium and demonstrated that thrombin itself inactivates prothrombin. Thrombin as a hemostatic agent was investigated by Warner and his associates³³¹. These authors recommend it as a suitable coagulant for local application.

Ferguson and Erickson³³² demonstrated that cephalin and calcium increase the clotting power of trypsin, although trypsin alone is active. On the basis of this work and other experiments, these same authors³³² pointed out that the absence of this "clotting enzyme" in the blood of

323 Volker, J. F. The Effect of Saliva on Blood Coagulation, *Am J Orthodontics* **25** 277, 1939.

324 Putnam, T. J., and Hoefer, P. F. A. Cysteine Hydrochloride as an Anti-coagulant for Clinical Use, *Am J M Sc* **198**:502, 1939.

325 Astrup, T. Heparin and the Inhibition of Blood Clotting, *Science* **90** 36, 1939.

326 Lucia, S. P., and Aggeler, P. M. Heparin and the Blood Coagulation Mechanism, *Proc Soc Exper Biol & Med* **40** 41, 1939.

327 Milliken, L. F. The Use of a New Blood Coagulant in Transurethral Prostatic Resection, *J Urol* **42** 75, 1939.

328 Schumann, E. A. Newer Concepts of Blood Coagulation and the Control of Hemorrhage, *Am J Obst & Gynec* **38** 1002, 1939.

329 Copley, A. L. On the Specificity of Thrombin Action, *Am J Physiol* **126** 310, 1939.

330 Mertz, E. T., Seegers, W. H., and Smith, H. P. Inactivation of Prothrombin by Purified Thrombin Solutions, *Proc Soc Exper Biol & Med* **41** 657, 1939.

331 Warner, E. D., Brinkhous, K. M., Seegers, W. H., and Smith, H. P. Further Experience with the Use of Thrombin as a Hemostatic Agent, *Proc Soc Exper Biol & Med* **41** 655, 1939.

332 Ferguson, J. H., and Erickson, B. N. Calcium and Cephalin in Relation to the Clotting Power of Crystalline Trypsin, *Proc Soc Exper Biol & Med* **40** 625, 1939, A New Clotting Factor and Its Possible Relationship to Hemophilia, *Univ Hosp Bull, Ann Arbor* **5** 45, 1939.

hemophiliacs could well account for the delayed clotting. Brinkhous³³³ also studied the clotting defect in hemophilia and concludes that it was the result of delayed thrombin formation.

A most interesting case of abnormal bleeding is described by Schonholzer.³³⁴ The patient was a young boy who since birth had had multiple diffuse recurring hemorrhages. The blood showed a prolonged clotting time. The boy's grandfather died from hemorrhages, one of his sisters had died at the age of 17 days from an umbilical hemorrhage, the blood of another sister, aged 15 years, had a clotting time of twenty-one minutes. Examination of the patient's blood revealed absence of fibrinogen.

BANTI'S SYNDROME

The etiology of splenomegaly has been carefully studied by Rousselot and Thompson.³³⁵ These authors produced progressive hepatic cirrhosis in dogs by multiple intravenous injections of silicious particles over a long period. Microscopically the liver showed definite cirrhotic changes. Studies on the venous pressure of living dogs revealed definite hypertension in the splenic vein. This observation substantiated a previous report by these investigators on the occurrence of hypertension in the lienal vein of patients with so-called Banti's disease. In addition to the aforementioned conditions, the dogs had congestive splenomegaly, anemia and thrombopenia, and in 1 instance esophageal varices were found.

Rousselot³³⁶ reviewed 14 cases of Banti's syndrome. He noted portal stasis and increased venous pressure. The splenomegaly present was secondary to the congestion. There are several factors which may produce congestive splenomegaly. It is most important to know the exact cause of enlargement of the spleen to determine whether it should be removed surgically. In the author's opinion, removal of the spleen should not be attempted if severe disease of the liver is present. In regard to the question of splenectomy, Collins³³⁷ states that the operation may be of some value if performed early in the course of the disease, but the indications are not definite. He also stresses the fact that the spleen should not be removed if portal cirrhosis is present. Splenectomy

333 Brinkhous, K. M. A Study of the Clotting Defect in Hemophilia. The Delayed Formation of Thrombin, *Am J M Sc* **198**:509, 1939.

334 Schonholzer, G. Die hereditäre Fibrinogenopenie, *Deutsches Arch f Klin Med* **184**:496, 1939.

335 Rousselot, L. M., and Thompson, W. P. Experimental Production of Congestive Splenomegaly, *Proc Soc Exper Biol & Med* **40**:705, 1939, The Experimental Production of Congestive Splenomegaly, *J Clin Investigation* **18**:473, 1939.

336 Rousselot, L. M. Congestive Splenomegaly (Banti's Syndrome), *Bull New York Acad Med* **15**:188, 1939.

337 Collins, D. C. The Value of Splenectomy, *West J Surg* **46**:628, 1938.

is recommended by Chamberlain³³⁸ at any time, but preferably early in the course of the disease, as the mortality rate increases with the duration of the disease. Jones,³³⁹ in his report on unusual cases of splenic disease, reports an occasional case of Banti's disease in which the patient survived splenectomy. It is difficult to evaluate this paper, as one cannot be sure of the type of case reported.

Andrus and Holman³⁴⁰ readily admit that Banti's disease does not exist, yet they recommend surgical intervention. They further report a high mortality rate. Hepatic schistosomiasis simulating Banti's disease is reported by Ippolito and Boyd.³⁴¹ The patient, a young woman, underwent splenectomy and died. The authors recommended this form of therapy in an effort to prevent the occurrence of degenerative changes in the liver. Schousboe³⁴² believes that splenomegaly (proliferation of the reticuloendothelial tissue) as observed in Banti's disease inhibits normal erythropoiesis and leukopoiesis. As a result there are anemia, leukopenia, thrombopenia and hyperplasia of the bone marrow. Splenectomy, according to the author, is followed by a return to normal of the hemopoietic functions. Stahr³⁴³ observed 3 cases of splenomegaly associated with syphilis. The patients responded poorly to antisyphilitic therapy, hence splenectomy was performed, with excellent results for one year. Further information concerning the patients was not available.

INFECTIOUS MONONUCLEOSIS

In our previous reviews the historical aspect of infectious mononucleosis was fully discussed. Paul³⁴⁴ has recently summarized the important clinical features. He states that the disease usually occurs in young adults who live a sedentary life. The presenting symptoms are sore throat, malaise, pain in the shoulders and neck, irregular fever, chilly sensations and enlarged glands. Marshall³⁴⁵ emphasizes the mental symptoms which may be observed occasionally. The physical signs encountered are enlarged glands, an enlarged spleen, oral lesions, ocular tenderness, puffy eyelids and a maculopapular rash. Spleno-

338 Chamberlain, D. Surgical Conditions of the Spleen, *Clin J* **68** 182, 1939.

339 Jones, A. P. Unusual Spleen Cases, *Ann Surg* **109** 960, 1939.

340 Andrus, W. D., and Holman, C. W. Splenectomy in Various Blood Disorders, *Ann Surg* **109** 64, 1939.

341 Ippolito, T., and Boyd, L. J. Hepatic Schistosomiasis, *Bull New York M Coll* **2** 12, 1939.

342 Schousboe, J. Two Cases of Inhibition of Bone Marrow Due to Splenomegaly, *Nord med (Hospitalstid)* **2** 1980, 1939.

343 Stahr, G. E. Splenectomy for Gastric Hemorrhage in Splenomegaly Associated with Syphilis, *U S Nav M Bull* **37** 256, 1939.

344 Paul, J. R. Infectious Mononucleosis, *Bull New York Acad Med* **15** 43, 1939.

345 Marshall, E. A. Infectious Mononucleosis, *Am J Clin Path* **9** 298, 1939.

megaly was present in 50 per cent of the patients examined by Marshall Templeton and Sutherland³⁴⁶ observed cutaneous lesions in 185 per cent of their series of 91 cases. The eruption was maculopapular, had the appearance of German measles, was usually limited to the trunk and face and was at times associated with pruritus. This rash may appear between the third and the twentieth day, it lasts three to seven days and does not desquamate.

In the early course of the disease leukopenia may be present, and this is followed by leukocytosis. The differential count shows a predominance of characteristic lymphocytes. Bowcock³⁴⁷ describes blast cells in the peripheral blood and emphasizes the fact that their presence may complicate the diagnosis. The heterophil antibody test, as is pointed out by Paul, gives a positive result in more than 90 per cent of the cases. The temporarily positive Kahn and Wassermann reactions which may often be seen have been the subject of study by Sadusk³⁴⁸ and Saphir.³⁴⁹ Sadusk points out that there is no direct correlation between the false positive reactions and the heterophil antibody test. In his opinion the positive Kahn and Wassermann reactions would be seen more frequently if serial tests were done. Saphir emphasizes the fact that the cause of the false positive reactions is not known.

A most interesting observation of the simultaneous occurrence in the same patient of typhoid fever and infectious mononucleosis is reported by Schwartz and Lidman.³⁵⁰ Since these diseases simulate each other in many respects, the differential diagnosis presented many problems.

The cause of infectious mononucleosis is still the subject of controversy. Pons and Julianelle,³⁵¹ in a series of articles, describe the isolation of *Listerella monocytogenes*, its identification and the immunologic and serologic reactions associated with it. The organism is a small gram-positive rod and grows in small colonies when plated. The organism obtained from the blood, when injected into rabbits, guinea pigs and

346 Templeton, H. J., and Sutherland, R. T. The Exanthem of Acute Mononucleosis, *J. A. M. A.* **113** 1215 (Sept. 23) 1939.

347 Bowcock, H. Mitotic Leukoblasts in the Peripheral Blood in Infectious Mononucleosis, *Am. J. M. Sc.* **198** 384, 1939.

348 Sadusk, J. F., Jr. Temporarily Positive Kahn and Wassermann Reactions in Infectious Mononucleosis, *J. A. M. A.* **112** 1682 (April 29) 1939.

349 Saphir, W. The Wassermann Reaction in Infectious Mononucleosis, *Am. J. Clin. Path.* **9** 306, 1939.

350 Schwartz, A. S., and Lidman, B. Infectious Mononucleosis Complicating Typhoid Fever, *Ann. Int. Med.* **13** 895, 1939.

351 Pons, C. A., and Julianelle, L. A. Isolation of *Listerella Monocytogenes* from Infectious Mononucleosis, *Proc. Soc. Exper. Biol. & Med.* **40** 360, 1939, Identification of *Listerella Monocytogenes*, *ibid.* **40** 362, 1939, Immunological and Serological Reactions of *Listerella Monocytogenes*, *ibid.* **40** 364, 1939.

white mice, produced typical lymphocytic-monocytic changes in the blood, and the animals died. When eighteen to twenty-four hour cultures are applied either by instillation or by heavy suspensions into the conjunctival sacs or (by swabbing) on the everted conjunctivas of rabbits, they produce characteristic changes which cannot be elicited or duplicated by any other organism. Antiserums prepared from the various strains which the authors isolated revealed two types, designated I and II. The former was composed of two rabbit and two human strains, and the latter was composed of one strain each from the cow, the sheep and the goat. From their results the authors conclude that immunity to infection is broader than type differentiation as demonstrated by agglutination. Animals with conjunctivitis were immune to similar infections, but intravenous immunization did not offer the same protection.

Wising³⁵² removed glands from 3 patients with infectious mononucleosis during the febrile stage. Emulsions and, later, antigens were made from this material. No organisms were recognized either microscopically or by cultivation. When these antigens were injected either intracerebrally or intracutaneously into monkeys, fever, enlarged glands and changes in the blood simulating infectious mononucleosis were observed. Emulsions obtained from these glands and injected into other monkeys produced similar results. During the course of these experiments one investigator accidentally inoculated himself, and he subsequently had what the author believes was true infectious mononucleosis.

The prognosis of infectious mononucleosis is good. The disease is self limited and usually runs its full course in two to four weeks. No specific therapy is known. Stannus and Findlay³⁵³ report what they believe is the first case of treatment with sulfapyridine. From all the facts known concerning the disease and the drug, the advisability of general use of the latter for this condition may be questioned.

352 Wising, P. J. Some Experiments with Lymph Gland Material from Cases of Infectious Mononucleosis, *Acta med Scandinav* 98 328, 1939.

353 Stannus, H. S., and Findlay, G. M. Mononucleosis, Acute Infectious Treatment with Sulfapyridine, *Lancet* 2 595, 1939.

News and Comment

American Congress of Physical Therapy—The nineteenth annual scientific and clinical session of the American Congress of Physical Therapy will be held Sept 2-6, 1940, at the Hotel Statler, Cleveland. The mornings will be devoted to an annual instruction and the afternoons and evenings to scientific sessions. There will be symposiums dealing with light, heat and electricity as important therapeutic adjuvants in general medical and surgical practice.

Further information may be procured by writing directly to the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

Recently Established Periodicals

Archives balkaniques de médecine chirurgie et leurs spécialités. A quarterly, edited by J Chryssikos, M Yoel and A Hadjigeorges and published by Masson & Cie, Paris, France. The publication of this journal was begun in 1939.

Boletín del Hospital oftalmológico de Ntra Sra de la Luz. A bimonthly, edited by Dr A Torres Estrada and published by Hospital de Ntra Sra de la Luz, Ezequiel Montes, 135, Mexico, D F. The first issue was for January-February 1940.

Revista cubana de obstetricia y ginecologia. A monthly, edited by Prof Jose Ramírez Olivella and published in Habana, Cuba. The first issue was published October 1939.

Revista medica militar. A bimonthly, published by Sanidad Militar in Mexico, D F. The first issue was published in 1939, the last one in hand covers four months, November and December 1939 and January and February 1940.

Revista mexicana de tuberculosis y enfermedades del aparato respiratorio. A bimonthly, edited by Dr Donato G Alarcón and published in Mexico, D F. The first issue was for July-August 1939.

CORRECTION

In the article by Dr Francis M Rackemann entitled "Allergy: A Review of the Literature of 1939," in the January issue (*ARCH INT MED* 65 185, 1940), the second sentence of the second paragraph on page 199 should read: "Of 83 consecutive asthmatic patients who were subjected to bronchoscopy at the Clinic, 33 patients (40 per cent) were found to have definite stenosis of one or, occasionally, more of the bronchi."

Book Reviews

Die Eiweisskörper des Blutplasmas By H Bennhold, E Kylin and St Rusznyák Price, 40 marks Pp 476, with 59 illustrations Dicsden Theodor Steinkopff, 1938

The book is a collection and synthetic evaluation of the dispersed accumulation of data concerning the proteins of the blood plasma It has two main divisions a general and a clinical one In reviewing a new venture such as this one, it may be best to furnish the reader an idea of the scope of the undertaking by enumerating the chapters and the names of the writers thereof, all of whom have been prominent workers in their respective fields

The first chapter of the general section, by R E Liesegang, deals with fundamental physicochemical conceptions One of the main features of the whole book becomes evident in this chapter The preponderant consideration of the physicochemical aspects of the problem A chapter with a more comprehensive treatment of the chemistry of the plasma proteins might not be an unwelcome addition to this book

In the second chapter E Kylin considers the fundamental physiologic conceptions of the plasma proteins Here, as in other chapters, it is stressed that the methods of separating the various protein fractions usually alter the proteins as they occur in the blood, although it is not denied that much useful information has been obtained by the employment of such methods The newer methods of identification by means of the ultracentrifuge and by cataphoresis constitute an advance in this direction However, it would seem rather difficult to decide anything as to the occurrence of different kinds of fibrinogen, for instance, and their possible functions in vivo by cataphoretic experiments with a plasma of a p_H as high as 12.4 From analogy, it would be expected that at such a degree of alkalinity ammonia would be liberated from protein, producing changes even greater than those obtained by salting out

In the third chapter, Jurgens discusses the origin of the plasma proteins He favors the view that they originate where the formed elements of the blood are produced He emphatically states that the liver cannot be regarded as the sole source of any of the plasma proteins

In the fourth chapter, Hatz provides a critical review of various methods of determination of the blood proteins In the fifth, Geill treats of the precipitation of the blood proteins by means of the salts of the light and heavy metals It is justly stressed that the complete reversibility of the precipitation with the light metal salts can be expected only when a number of conditions are realized Enlargement of the chapter, particularly with regard to the precipitation by other agents, such as alcohol and acetone, which when employed under proper conditions yield soluble precipitates, may not be amiss

The sixth chapter, "The Colloid Pressure of the Blood," has been entrusted to von Farkas, who prefers the term "colloid pressure of the blood" to "colloid osmotic pressure" or "oncotic pressure" Needless to say, this chapter contains much of great interest The more surprising it is that the "*Leberspore*" in man is accepted as if no very weighty objection to it had ever been raised It is also stated that Nonnenbruch calls attention to the fact that even the capillaries of the extremities are entirely impermeable to protein The work of Drinker and his co-workers, dealing with this subject, deserves some consideration and more than it has received in other chapters of this book The writer of this chapter thinks that a neurohormonal regulation of the colloid pressure may be assumed to exist, though its existence is not yet proved As in a later chapter by Rusznyák, the importance of water and sodium chloride for the production of edema is stressed by von Farkas

In the seventh chapter, Bennhold treats of the transporting function of the blood proteins. This function of the blood proteins, to the knowledge of which Bennhold has contributed so much, has not yet received the consideration it demands from the physician, so it may be well to call attention briefly to the "embatic" effect. A coarsely dispersed acid dye (such as, for instance, Congo red) in watery solution, placed over a 5 per cent gelatin gel, does not penetrate into the gel, whereas, when it is added to serum it does penetrate into the gel as far as the serum albumin.

Furthermore, various substances—the regular constituents of the organism, such as bilirubin or bodies foreign to it—travel in the electric field, some with the albumin and some with the globulin fractions and others free. The results are summarized in a table. More or less firm combinations with the proteins may be formed, and the substances may be unloaded in different organs, whereby different forces may exert themselves. An exception may be taken to the fact that the author calls the structural chemical difference between coproporphyrin and uroporphyrin a minimal one. The first attaches itself to albumin and the latter does not, but there is a difference of four carbonyl groups in favor of uroporphyrin, as given in the formulas. Without detracting from the other contributors, this particular chapter is perhaps the most stimulating one of the book. It forms the concluding chapter of the general section, which comprises 303 of the 470 pages of the book.

The first chapter of the clinical section of the book gives the normal and pathologic limits of the proteins as compiled by Hath and Koranyi, with the methods of their determination. The second chapter of this section deals with the relation of the plasma proteins to edema. Here Rusznyak emphasizes the importance of the diminished colloid osmotic pressure in addition to that of the venous pressure. Thus, for instance, in the presence of cardiac edemas the colloid osmotic pressure is normal but the venous pressure is high, whereas in the nephrotic type of edema the colloid osmotic pressure is low, and the venous pressure is normal.

In chapter 3 the relation of the plasma proteins to albuminuria is discussed by Koranyi. The conclusion is reached that albuminuria in cases of renal disease, as well as in febrile conditions, is due to an increased permeability of the glomerulus and not to a pathologic change in the plasma proteins. The normal glomerulus passes proteins of less than 70,000 molecular weight, and the diseased glomerulus does this more readily.

In the fourth chapter the relation of serum protein to serologic reactions is discussed by Klinke. The subject also is treated mainly from the colloid chemical standpoint, with little reference to the clinical aspect. This deficiency, it may be stated here, is shared with the other chapters of this section.

In the fifth chapter, Kylin gives pathologic protein reactions to the blood. Here the sedimentation rate of the red blood corpuscles is discussed. The relation to fibrinogen and to the globulins is shown, and it is pointed out that with an increase in these proteins the sedimentation rate increases to a greater extent than does the concentration of the proteins. For the clinical evaluation of the sedimentation rate, the reader is referred to the book of Reichel. The Takata test, the "formol-gel" test and other tests also are treated from the standpoint of their relation to the proteins rather than from that of their clinical applications.

The sixth chapter, by Klinke, on plasma protein and the coagulation of blood, concerns itself with the mechanism of the coagulation and retraction of the clot.

In the seventh, and last, chapter, a summary of the significance of the plasma protein in its clinical application is attempted by Kylin. The discussion is based on the conception that the plasma proteins are to be considered as an organ, a conception first advanced by Bennhold. Thus, for instance, a subheading is "The Diseases of the Organ of the Plasma Proteins." With reference to the red blood corpuscles the distinctions are (1) too few red blood cells (anemia), (2) too many red blood cells (polyglobulic) and (3) a pathologic form of red blood cells (poikilocytosis) in which 1 and 3 are often combined.

With reference to the white blood cells we have (1) too few white blood cells (leukopenia), (2) too many white blood cells (leukemia) and (3) a pathologic form of white blood cells (2 and 3 are often combined)

With reference to the plasma proteins there are (1) diseases with hypoproteinemia (hypofibrinogenemia, hypoglobulinemia and hypoalbuminemia), (2) diseases with hyperproteinemia (hyperfibrinogenemia, hyperglobulinemia and hyperalbuminemia) and (3) diseases with pathologic plasma proteins

The conception of the plasma proteins as an organ is justified on the contention that an organ is a part of the body having a special function. However, according to this definition, connective tissue would be an organ, as also would peripheral nerves and other structures. Whether the conception of the plasma proteins as an organ in this sense will find favor is questionable. Here it may be sufficient to state that the book has succeeded in its main purpose, which is to give a somewhat organic connection to more or less isolated facts. The book is stimulating and is certainly to be recommended to the physician who does not demand an immediate, clearcut application in his everyday practice.

Anemia in Practice By William P. Murphy, A. B., M. D. Price, \$5.00, cloth. Pp. 344, with 46 illustrations. Philadelphia: W. B. Saunders Company, 1939.

In the preface Murphy states: "For several years it has been my desire to assemble the vital information concerning the anemias which is now at hand." Paraphrasing this quotation, there has been a great deal of productivity in the field of hematology in the last fifteen years, which has resulted in a great increment to the knowledge of the anemias. This is particularly true of pernicious anemia. The author is responsible for a goodly part of the information that has been obtained. Because of his intensive work in the problems of anemia and because of his large clinical experience, Murphy is well equipped to prepare this monograph. It need hardly be added that on account of the author's interest in pernicious anemia the book is almost entirely devoted to this particular type of blood dyscrasia. Illustrating this statement is the fact that part 1, some 64 pages, is devoted to the classification and diagnosis of the hypochromic anemias and their treatment and to the normocytic anemias and their treatment, whereas part 2, which has to do with pernicious anemia, is some 200 pages in length.

The section devoted to pernicious anemia first devotes a few pages to the historic aspects of the disease. Then it deals with the diagnosis. Murphy then discusses the mechanism of red cell formation under normal and abnormal circumstances. To liver therapy are devoted four chapters. Succeeding chapters have to do with the prognosis, incidence, complications, differential diagnosis and practical management of the patient. The last 50 pages of the book dwell on laboratory procedures and blood transfusion.

Only a few comments seem appropriate. Murphy is so familiar with his subject from personal observation and has so thoroughly covered the literature that little can be added. Certainly nothing unfavorable can or need be said concerning the subject matter of this book in so far as it applies to pernicious anemia. On the other hand, the discussion of anemias other than pernicious anemia seems to be quite sketchy and somewhat inadequate.

I am glad to find that Murphy believes in the use of the hematocrit but confines hematocrit studies to determining the mean corpuscular volume of the red cells, the simplest method of determining increase in the size of the cells. He implies that in the absence of achlorhydria the diagnosis of pernicious anemia may well be questioned. He believes that the parenteral administration of liver is the therapy of choice and that the patient should continually receive a maintenance dose with the minimum amount of difficulty or trouble.

It hardly seems appropriate to put in a book which represents so much deep scientific thought and remarkable series of clinical studies, illustrations which would appeal to the mind of a 10 year old child. To see little one-lined men pouring material into a stomach certainly does not attribute much intelligence to the reader.

Principles of Hematology with 100 Illustrative Cases By Russell L Haden, M A, M D Price, \$4 50, cloth Pp 348, with 155 illustrations Philadelphia Lea & Febiger, 1939

In this monograph Haden discusses first the formation of blood, taking up the embryologic as well as the physiologic considerations in some detail Succeeding chapters have to do with the leukocytes, the thrombocytes and the technic of examination of the blood The next three chapters dwell on the mechanism of production of various abnormalities of the blood, the word "abnormalities" being used in its broader sense The explanation of the mechanism of leukocytosis and leukopenia, for example, is most interesting and informative Treatment of the hematic disorders then follows This completes the formal presentation of the subject of hematology

The remaining eleven chapters are particularly to be commended In them, approximately one third of the book, is a series of case reports covering succinctly and clearly all the various types of anemia, such as polycythemias, leukocytoses and leukemias This section makes interesting reading and explains clearly the rather dogmatic, didactic first two thirds of the book

The book is well illustrated with photomicrographs It is one of the pleasant features of the volume that there are no colored plates of the blood, which are so frequently poorly reproduced and inaccurately colored There is a wealth of diagrams which add materially to the understanding of the printed word These may seem rather elementary, but to the student or to a man who is not primarily interested in hematology they will be of inestimable value

Haden, like most present day clinical hematologists, stresses the importance of hematocrit readings in the study of disorders of the blood Some of the more complicated formulas that he has devised are mentioned, but, as reflected in the case reports, most of them are discarded after the primary description of how to obtain them and what they imply The mean cell volume, the most important observation of the hematocrit reading, is not neglected

The book is to be recommended most highly Unless one is thoroughly familiar with hematology it will prove of great everyday service to the man who is coming in contact with patients suffering from hematologic disorders, and nearly every person who is sick does have some disturbance of the red cells, of the hemoglobin, of the white cells or even of the thrombocytes

Classic Descriptions of Disease Ralph H Major, M D, Professor of Medicine, The University of Kansas Second Edition Price, 5 50 Pp 727 Springfield, Ill, and Baltimore Charles C Thomas, Publisher, 1938

In this book four hundred original accounts of disease are presented in English with pertinent material relative to the history of the disease and brief biographies of the various authors For example, when dealing with diabetes mellitus Major selects the following accounts that of the Papyrus Ebers (1500 B C), the fascinating descriptions of Aretaeus (second century A D), the article of Willis (dealing with the sweet taste of the urine), Kussmaul's account of air hunger and diabetic coma, Mering and Minkowski's observations on the production of experimental diabetes by pancreatectomy, Opie's description of the hyaline degeneration of the islets of Langerhans and finally the announcement of Banting and Best of the successful extraction of the internal secretion of the pancreas from degenerated pancreatic tissue There are sections dealing with infectious diseases, metabolic diseases, lead poisoning, diseases of the circulatory system, diseases of the blood, kidney disease, respiratory diseases, deficiency diseases, allergic diseases and diseases of the digestive tract For obvious reasons, in the compilation of such an anthology not all the diseases selected could be presented completely or dramatically In the selection of his material Major tried to choose "either the first known, one of the earliest or one of the most interesting accounts of the disease

in question" No attempt was made to consider all diseases with equal completeness, "since some diseases have more interesting and more extended histories than others and also because of personal taste, or bias if you will, in the selection of authors"

In the preparation of this work Major had in mind the value of approaching the history of medicine from the clinician's point of view Thus, he begins with a disease and leads the reader back to the various personalities that contributed to our knowledge of it, instead of introducing a famous character and commenting on the various diseases that the savant happened to be interested in Consequently, the book helps bridge the gap between the cursory history of diseases that is given in the ordinary history of medicine and the formal histories of medicine that are predominantly biographic

Technically, the standard of printing is high The book is easily handled and will make a valuable addition to the library of any one directly or even remotely interested in medicine

The second edition has been improved by the addition of material on yellow fever and malaria, the revision of various biographic sketches and the incorporation of additional readings and illustrations

Menstrual Disorders Pathology, Diagnosis and Treatment By C Frederic Fluhmann, M D, C M Pp 329, with 119 illustrations Philadelphia W B Saunders Company, 1939 Price, \$5

In this excellent volume is presented not only a fine discussion of menstrual disorders but a minute, concise description of the normal menstrual cycle The intricate interrelationships of the hormones concerned in menstruation and the results of disturbed mechanism of these hormones as reflected in uterine bleeding are discussed in detail and presented clearly and comprehensively The author's classification of menstrual disorders and abnormal uterine hemorrhage is excellent and serves as a good working basis for clinical diagnosis The chapter on dysmenorrhea is particularly recommended Bleeding as a result of pathologic pelvic conditions is discussed remarkably well, and the reasons for the bleeding associated with these conditions are clearly explained from the viewpoint of both pathologic findings and pathologic function

The value of this book is enhanced by the abundance of excellent photomicrographs and charts, the majority of the latter being original

This volume contains a wealth of information and should prove of immeasurable value not only to the gynecologist but to any one who is concerned with the care of female patients The style and composition are such as to make the book easily understandable to the average medical student

Short Stature and Height Increase By C J Gerling Price, \$3 00 Pp 159 New York Harvest House, 1939

This book, written for the laity, is motivated by the thesis that the person who happens to be of short height is unfortunate in his contacts with other people The author points out that the big man has the advantage in more ways than one over the short man Furthermore, the short person feels that he is at a disadvantage and often is truculent and self assertive The purpose of the book is to sketch how the person may overcome the handicap of short stature Gerling suggests measures which may have some effect on the height of the adult Although there is little that can be done to increase height, by maintaining a good posture, which is built up by exercises, the short person is able to take care of his defect to a certain extent Also, such customs as wearing garments which give the appearance of height, elevating the heels of the shoes, avoiding smoking large cigars and pipes and wearing a mustache may give a certain amount of spurious increase in height which would be of psychologic help to the small man

The book is written in an attractive style and should be of great interest to the short person. The advice for the most part is sane, sensible and easy to follow. The doctor may cause gratitude in the heart of his patient small in stature if he recommends the book to him.

The Patient as a Person. A Study of the Social Aspects of Illness. By George Canby Robinson. Price, \$3.00. Pp 423. New York: Commonwealth Fund, Division of Publications, 1939.

Dr. Robinson has written an interesting book which I hope will be widely read and will do some good. In these days when there is great effort to make diagnoses purely from laboratory and roentgenologic reports, there is much need for protesting books like this which show how often a serious situational neurosis complicates organic disease and perhaps makes successful treatment impossible. This is probably particularly true in the case of clinic patients, but it is almost as true of patients of the middle and upper economic classes, who are commonly unhappy, worried, overworked or psychopathic.

The book is made up almost entirely of well abstracted case reports in which only essential points are given. It should be read by all young physicians starting out in practice, and it should of course be read by all students who plan to be social service workers.

The Physiology and Pharmacology of the Pituitary Body. Volume II. By H. B. Van Dyke, M.D. Price, \$4.50. Pp xiv + 402, with 28 illustrations and 10 tables. Chicago: University of Chicago Press, 1939.

The first volume of this book was published in 1936 and was reviewed favorably in the *ARCHIVES OF INTERNAL MEDICINE* (60:248 [Nov.] 1937). The second volume also deserves much praise. It continues with a critical review of the history of research on the pituitary body from 1935 until 1938 and represents a sifting and classifying of all recent work on the physiology and pharmacology of this peculiar gland. The bibliography contains 1,418 titles, which the author states represent only 78 per cent of the articles which were considered.

Inevitably, the two volumes together will prove of great usefulness to all students, investigators and clinicians who have any interest in modern endocrinology.

Landmarks in Medicine. By various authors, with an introduction by James Alexander Miller, President, New York Academy of Medicine. Price, \$2.00. Pp 347 with 15 illustrations. New York: D. Appleton-Century Company, Inc., 1939.

This is one of the series of books promoted by the New York Academy of Medicine and containing lay lectures on medical subjects. These books are most interesting and valuable from a historical point of view and in addition make delightful reading. It is difficult to place one lecture above another in interest and value, but it is worth a wager that the majority of readers will turn first to Martland's "Dr. Watson and Mr. Holmes." Other contributors are Francis R. Packard, Alfred E. Cohn, James J. Walsh, Raymond Pearl, Reginald Burbank and Lewis Gregory Cole.

Les cholécystites chroniques. By A. Danes. Preface de J. Rieux. Price, 38 francs, paper. Pp 118, with 11 illustrations. Paris: Gaston Doin & Cie, 1937.

This is a brief monograph on chronic cholecystitis. It is entirely a clinical study and largely nontheoretic, and is presented as "a practical guide for the general practitioner." The author reviews clearly the more elaborate experimental contributions that have been made in the field it covers, particularly in the study of the diseased gallbladder, and translates these studies into simpler observations,

which can be made at the bedside for the most part. The book will be of interest to those who read French and will prove instructive to those who are primarily interested in disease of the gallbladder, be they surgeons or internists.

Herz-und Kreislaufferkrankungen in ihren Beziehungen zum Nervensystem und zur Psyche By H. D. von Witzleben. Price 4.50 marks. Pp 101. Leipzig: Georg Thieme, 1939.

This little book consists in essence of a review of the physiology of the circulation, with comments on abnormal conditions, such as hypertension. However, with hypertension, for example, there is no thorough discussion of current views as to humoral pressor substances. In general, moreover, the book lacks adequate documentation. There are no references and no index. It is, however, well written and makes interesting and stimulating reading.

Epidemic Encephalitis Third report by the Matheson Commission (Willard C. Rappelye, Chairman). Price, \$3. Pp 493, with 33 tables and 4 charts. New York: Columbia University Press, 1939.

This critical and authoritative summary of the problem of encephalitis is a timely contribution to a subject important to all physicians. The bibliography, occupying nearly three hundred pages, is in itself a valuable piece of work. Current theories on causes of the various types of encephalitis, treatment and epidemiology are all discussed, with the aid of many pertinent tables and charts.

Harvey Cushing's Seventieth Birthday Party By the Harvey Cushing Society. Price \$3.00. Pp 146, with 9 illustrations. Springfield, Ill.: Charles C. Thomas, 1939.

There is in existence a Harvey Cushing Society comprised of some 47 active members—a group of men interested in various aspects of neurosurgery scattered all the way from New Orleans to Toronto, from San Francisco to Boston, and with corresponding members in Breslau, Manchester, Oxford, Paris and Stockholm. It is a lively little club, each member owing something of his accomplishments and ideals to Harvey Cushing. Thus, when this society held its eighth annual meeting in New Haven last April to celebrate Dr. Cushing's seventieth birthday, the occasion was not without significance. There were speeches and the drinking of healths, tributes, telegrams and letters from members who could not be there, and even more telegrams and letters from nonmembers who wished they were of the elect. On the whole, the occasion was a joyous one with a good deal of merriment.

This birthday party now has been perpetuated in book form. It is a gay, friendly little volume. Even from the pictures of the occasion one catches glimpses of Dr. Cushing's vitality. His own speech, of course, is characteristically graceful and charming. Graduates of the Hospital—to the alumni of Massachusetts General Hospital there can ever be but one Hospital—will enjoy the account of Dr. Cushing's career as "house pupil." This has been carefully described by Dr. Henry R. Viets with some interesting reproductions of the manner in which, even in those early days, Dr. Cushing kept his clinical records.

It does no harm to emphasize the human side of a great doctor. Dr. Cushing's friends as well as future medical historians will be glad of this unusual sidelight on his career.

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